# Banting Memorial Lecture, 1954
# Hormones of the Pituitary Posterior Lobe

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This lecture commemorates Frederick Grant Banting, his life and his work, bringing once again into the focus of our immediate attention the achievement for which the world will always keep his name in honor. There is no need, of course, for me to remind you, the members of a Diabetes Association, of this special reason for keeping him in grateful memory. There is no possibility that you will ever forget the enterprise which, some 33 years ago now, he led with such vigor and insistence, and with a youthful enthusiasm unblunted by experience. And there are others, of course, whose work we think of with Banting's, and who are still alive, to know that we remember. There is Charles Best, Banting's younger comrade and his full partner in the work which gave the first clear proof that insulin had a real existence, and that its extraction on a practical scale ought not to be beyond the reach of conservative methods, when these could be developed in detail. It is good to know that Professor Best, still at the height of his powers, is leading an eager team of his colleagues and pupils in Toronto, and fulfilling the brilliant promise of that early triumph, when he shared with Banting in the great discovery which we commemorate. There is J. B. Collip, too, whose work did much to speed the developments required to bring insulin within the range of practical and regular production, from ordinary, slaughterhouse pancreas. Professor Collip, we rejoice to know, is also still fully active, leading his own research team, and carrying an administrative burden for the new generation, as Dean of the Medical Faculty in London, Ontario. And there was J. J. R. Macleod, head of the Physiological Department in Toronto when the early work on insulin was done there, who was prompt to organize men of his own training into a team to hasten its practical development, as well as to begin the study of its significance for normal and fundamental physiology. Professor Macleod, however, afflicted by ill-health, returned later to his native Scotland, where he died some years ago.

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## DEVELOPMENTS OF INSULIN

I must not allow myself to be drawn into any attempt at a detailed account of all the further developments of insulin itself, or of the forms in which it has been made available for application, during all the years for which it has now been in use. There may be those among you who can recall with me practically the whole course of the remarkable changes, in the quantities as well as the qualities of the insulin which has been available for use, since the first human sufferers from diabetes were treated. From a visit made to Toronto in September, 1922, I myself remember the improvised apparatus with which insulin was then being extracted and filtered, in the basement of the old Physiological Department in Toronto. The resulting brownish, rather murky solution then contained only so small an amount of insulin from every pound of the pancreas extracted, that one might have supposed that the new prospect of life and health was being opened only to a very small minority of those who needed it, and to those few at a great cost; but all the members of the team working there on the problem with such devoted enthusiasm, and even I, as a mere onlooker, were already looking with confidence to improvements so effective and rapid, in the methods of extracting insulin from the raw material, and of purifying it after extraction, that this early restriction on its practical application would soon disappear.

It did so indeed, and even with a rapidity beyond all reasonable prediction. By the end of 1922, little more than three months after I first visited Toronto to report on the situation to our Medical Research Council in Britain, in a number of the centers in different countries, which by then were co-operating with the parent organization in Toronto, insulin was being obtained in yields a hundred times as great as those of the previous September. And you will know how, through the intervening years, successive discoveries and devices have further improved the situation, until insulin has become

available as a practically pure substance, freed from the last traces of other materials naturally adhering to it and complicating its action, and presented now either in simple solutions, or with its solubility and state of dispersion modified by various chemical and physical means, so as to adjust the speed and the persistence of its action to the needs, or even to the convenience, of the individual patient. A wonderful triumph indeed, and one of which the beneficial effects on the practical treatment of diabetes need no emphasis here. I could make a long list of contributions to it which would be worthy of particular mention; but, as it is not the main subject of my lecture, I must be content to remind you of two: one made by my greatly respected friend of many years, the late Professor John J. Abel, whose first production of insulin in crystalline form was one of the high peaks of achievement, in a long career of single-minded devotion to fundamental researches in pharmacology and biochemistry; and one by Dr. David Scott, of Toronto, who discovered that the crystalline insulin, as Professor Abel had obtained it, was an insulin salt of zinc—a discovery which made the crystallization of insulin an easy procedure, applicable on the largest scale, and thus opened the way to the manufacture of practically pure insulin, and eventually to its presentation for use as a range of suspensions of different microcrystalline forms.

## INSULIN AND PROGRESS IN ENDOCRINOLOGY

Insulin, with the romantic features of its discovery and later history, will certainly not be absent, then, from our minds, whenever we are commemorating Fred Banting. I find myself, however, in agreement with what I take to have been the view of several of those who have preceded me in lectures of this series. Their choice of subjects has indicated a feeling, which I certainly share, that we honor the memory of Banting's pioneer spirit most fittingly, and in a manner which he himself would have approved, not by recalling on every one of these occasions the details only of his own achievements, or even of more recent developments from them, but by turning our attention also to other enterprises in the general field of medical research, and preferably to such as are at present showing progress of a particularly interesting kind, and giving clear promise of important advances yet to come. On more than one earlier occasion I have suggested that the discovery of insulin, in addition to its dramatic and revolutionary affect on the practical treatment of diabetes, and its direct value for researches dealing with fundamental problems of metabolism, had an even wider influence on the progress of medical knowledge and resources, through the great encouragement which it gave to fresh, more courageous and more determined enterprise, especially in renewed researches on the other ductless glands. For, according to my own memories, the interest and the expectations which had been aroused, some thirty years earlier, in 1891, by Murray's successful treatment of deficiencies of the thyroid gland, by administering simple extracts, and then the crude dried substance of the gland itself, had been followed by a long period of discouragement. No comparable success had been obtained with other ductless glands, and it had even begun to be suspected that the function, of at least some of them, might be to get rid of harmful products of the body's activities, rather than to form recognizable hormones, or that, if there were such hormones, these might be stored in quantities so small, or be of so unstable a nature, as to make it forever impossible to extract them for study, or for the treatment of the relevant deficiencies by replacement. Such doubts had, of course, been often expressed with regard to the pancreas and the antidiabetic hormone, which had so long been regarded as a possible product of its Langerhans islets, but had resisted all the many attempts to extract it from them. When, therefore, all such doubts were at last resolved in this case, the quest for other hormones was taken up in a new and confident spirit of enterprise; with the result that, within relatively few years, effective extracts were prepared from the parathyroid glands by Collip, and from the cortex of the adrenal glands by Swingle and Piffner; and, of these achievements, the latter has been followed, in more recent years, by the astonishingly rapid sequence of further advances which have resulted in the isolation, the chemical identification and even, in many cases, the artificial production by synthesis, of a whole series of steroid hormones from this remarkable organ, the adrenal cortex; the most widely famous and therapeutically the most promising of these, so far, being cortisone and the related Substance F, with their remarkable effects on rheumatoid and allergic conditions—effects not yet, I think, fully understood, or related yet with certainty to the normal adrenal functions.

I must not allow myself, however, to be led too far from the subject which I had chosen for this lecture. My particular purpose is to bring to your notice today a number of facts concerning the so-called neural or posterior lobe of the pituitary body, and the extremely active substances which can be extracted from it, and which appear to be secreted from it into the blood, so as to function as hormones regulating important physio-

logical functions. You will understand that I am concerned with one only, and that the smaller of the two main parts of the pituitary body. There is, indeed, an even more fascinating and, at the same time, an even more complicated story to be told concerning the discoveries, still in active progress, of hormones formed and secreted by the larger, anterior, or glandular lobe of that organ, most of them producing their effects, not directly on functions of the body as a whole, but by stimulating, or otherwise controlling, the activities of most of the ductless and some of the other glands—hormones which act on, and through, the thyroid gland, the adrenal cortex, the pancreatic islets, the reproductive glands, the mammary glands, and so on. Again, however, I must resist the temptation to wander beyond the proper limits of my chosen theme. And, if no other restraint were in this instance sufficient, I should remind myself that I am speaking to you in San Francisco, in a neighborhood where so much of what is known about this anterior pituitary lobe, with its multiple endocrine functions, has been revealed by the world-famous researches of Professor H. M. Evans and his many and variously distinguished associates.

## EARLY STUDIES OF THE PITUITARY POSTERIOR LOBE

Let me come, then, without further distraction or delay, to the subject chosen for my lecture, concerning which our experimental knowledge began at a much earlier date. Such knowledge of the posterior lobe of the pituitary body, the so-called neurohypophysis, and of its active constituents, began, indeed, as long ago as 1895. Dr. George Oliver, an enterprising physician of Harrogate, used to spend some of his spare time during the winter months in experimenting on himself and his family with extracts from different animal organs, as obtained from the local butcher. In 1895, he had prevailed upon a naturally sceptical and reluctant Professor Schäfer, in London, at the conclusion of an experiment made for a different purpose, to inject an extract, which Oliver had made from suprarenal glands, into the vein of an anesthetized dog, and to observe the effect upon the arterial blood-pressure, which was being recorded. Dr. Oliver had his reward, and Professor Schäfer a welcome surprise. The remarkable activity thus disclosed was later located in the adrenal medulla by Professor Howell, and the substance responsible for it was, in due course, isolated and identified, and became known as epinephrine, or adrenaline, a substance of which the remarkable activities, and their connection with many bodily functions, and especially with those controlled by the sympathetic nervous system, have figured so prominently, in the years that have followed, over a wide range of physiological and medical investigations. Only a few months later, so that their first description of its action followed their paper on the suprarenal gland directly, in the same volume of the *Journal of Physiology,* Oliver and Schäfer also observed the comparably remarkable activity of an extract of the pituitary body. In this case again, they did not, in their first experiments, distinguish between the different lobes of the gland in making the extract for trial; they simply took the whole gland, and made an extract from it with water or glycerol, and injected a few cubic centimeters of this into the vein of an anesthetized dog. And, as had happened with the suprarenal extract, the injection caused a remarkable rise of the arterial blood-pressure, which was evidently due largely to contraction of the smaller arteries, since it involved no pronounced acceleration of the heart-beat, such as the suprarenal extract had produced. And, in this case again, it was Professor Howell who traced this immediate vasopressor activity to one of the two quite distinct parts of the pituitary body, finding that the substance producing it came entirely from the neural, or posterior lobe. This was not, in fact, what would naturally have been expected; for the larger anterior lobe had the kind of structure suggesting a glandular function, whereas the posterior, neural lobe, joined to the hypothalamic region of the brain by the infundibular stalk, had a structure which, at first sight, resembled that of the gray matter of the brain, a tangle, apparently, of nerve fibres and supporting neuroglia, with a few scattered cells, or 'pituitocytes,' rather than that of a secreting gland. Later it was suggested that the so-called pars intermedia, inserted, as it were, between the anterior and posterior lobes, and consisting of a compact layer of cells, was really responsible for forming the intensely active substances, which the posterior lobe yielded so readily to extraction. The experimental facts, however, gave no real support to this idea; the posterior, neural lobe itself, though its structure was so much like that of brain-matter, somehow yielded the very active extract; though none prepared from the brain in general, or from its gray matter, appeared to have any comparable activity. I shall have something more to say later about recent evidence concerning the manner of the origin of so intensely active a substance, or substances, from what had long appeared to be so unlikely a source.

So far, however, I have only taken you to 1895, nearly 60 years ago, when Oliver and Schäfer gave a first, undetailed description of this activity of their extracts

from the pituitary body. Perhaps I should say, rather, that we have reached 1899, when they published a second paper, confirming Howell's findings, that the pituitary pressor substance was obtainable only from the posterior lobe, and that a first, fully effective injection of it rendered an animal for a long time almost insensitive to a second, so that no pressor response comparable to the first was again obtainable from the same animal until after some hours.

## EFFECTS ON THE BLOOD PRESSURE AND URINARY EXCRETION

Two years later again, in 1901, Schäfer and Magnus, in further exploring the nature of the action of this same vasopressor pituitary substance, came across the fact that the blood vessels of the kidney, unlike those of other organs, showed only a temporary constriction when the extract was injected, and that the kidney then showed a prolonged expansion, accompanied by a greatly increased secretion of urine. Later experiments by Schäfer and Herring led them to suggest that this diuretic effect was due to a different constituent of the pituitary extract, from that which raised the arterial blood-pressure; and though I myself, a few years later, incidentally to some other observations, failed to confirm the difference on which they had based this opinion, the question, whether the two effects were due to the same or to different substances, still remained open till quite recently. We shall see, indeed, that the whole question of the nature of the diuretic effect is complicated, and its physiological importance to a large extent discounted, by the fact that it has only been observed as the result of relatively large doses, injected intravenously into animals in which an anesthetic has reduced the spontaneous excretory function of the kidney to a subnormal level. The important, physiological effect, produced by even much smaller doses of the posterior lobe extract, given either hypodermically or intravenously to normal, conscious animals, including man, was later found to be in the opposite direction; instead of accelerating the secretion of urine, it greatly delayed, even for some hours, suspended, what would otherwise have been a vigorous diuresis following the drinking of water; and this is, beyond doubt, the normal, characteristic, truly physiological effect of the posterior-lobe pituitary hormone on the secretion of urine.

## EFFECTS ON THE UTERUS

Before we consider further that practically important aspect of its action, however, I ought to mention yet another effect of the posterior-lobe extract, which gave me a direct interest in the properties of this remarkable organ, in that I myself first observed it almost by accident, and described it in 1906. I had been studying a then newly observed, but now long familiar effect of certain alkaloids of ergot, in reversing many of the stimulating actions of epinephrine (adrenaline), including its powerful vasoconstrictor, pressor action in the cat. It was, of course, important for me to know whether this reversal was specific to the action of epinephrine, or whether any other normally vasoconstrictor agent would also cause the arterial pressure to fall, by producing a vasodilatation, after ergotoxine had been given. The posterior-lobe pituitary extract suggested itself, as a particularly suitable agent for a test of this possibility. It was easy to show that its action was, in fact, unaltered; it still produced its normal, large pressor effect after ergotoxine, in a cat in which epinephrine now had only a vasodepressor action. Incidentally, this confirmed other evidence, in showing that the pituitary pressor action had no relation to that of any part of the nervous system. It also happened, however, that a cat in which I observed this contrast was in an early stage of pregnancy, and that I was recording the tone and rhythm of the plain muscle of its uterus, as well as its arterial blood-pressure; and ergotoxine had, in this case, reversed the response of the uterus also, to an injection of epinephrine, so that it now relaxed and lost its rhythm as the blood-pressure fell. The posterior-lobe pituitary extract, on the contrary, not only caused the blood-pressure still to rise, but exhibited a most powerful stimulant action on the muscular wall of the uterus—more powerful, indeed, than any which, till then, had been observed, with any of the substances reputed to have an action of that kind.

Here, then, was another and potentially an important activity of this remarkable extract. The results of a few additional experiments appeared to show that the stimulating effect on the muscular wall of the uterus was present in all animal species, and in all functional conditions in relation to pregnancy. This action naturally found a wide practical use in obstetrics. The uterus of the guinea-pig, on which epinephrine had not been observed to exercise a stimulating action in any functional condition, always responded by contraction, and apparently showed a specially regular sensitiveness, to the stimulus of the pituitary extract. And, since the action upon the uterus and that on the blood-pressure seemed to bear a sufficiently constant proportion to one another, even in extracts differing widely with respect to their absolute activities in either of these directions, the

response of the uterus of a young, virgin guinea-pig seemed to give a convenient general measure of the activity of any posterior-lobe pituitary extract, if compared to that of a standard, prepared from the stabilized, dried material of perfectly fresh posterior lobes of the pituitary glands of oxen. And, for the time, the question whether the action on the uterus and that on the blood-pressure were due to the same, or to different active principles, had to be left open. The philosophical principle known as William of Occam's razor—*entia non multiplicanda praeter necessitatem*—seemed to me at that time to give a sufficient warrant for a provisional assumption that there was only one, unless and until there should be evidence for more than one.

## ANTI-DIURETIC ACTION OF THE POSTERIOR PITUITARY HORMONE

Meanwhile, however, there had been the new development of knowledge of which I have already made brief mention, concerning the relation of the pituitary posterior lobe to the excretory function of the kidney. Shortly before the first world war, in 1912 and 1913, and shortly after it again, from 1921 onwards, evidence began to accumulate for this other remarkable activity of the extract; when given hypodermically, even in a small dose, to a conscious animal of any species, including man, it reduced to small dimensions—if the dose was substantial it delayed for five or six hours—the output of urine by the kidney, which otherwise regularly followed the drinking of water. Such urine as was formed, while the influence persisted, was correspondingly concentrated, so that it was the excretion of water which was principally affected.

The evidence concerning the results of operative interference with the pituitary posterior lobe seemed at that time to be variable, and even conflicting; but this can be attributed partly to the lack of knowledge then of the very special relation of the lobe to certain nuclei in the brain, from which it receives its rich nerve supply, and partly to a tendency to interpret effects in the light of Schäfer's description of a diuretic action, and thus to assume that the normal endocrine function of the lobe was to promote, rather than to restrain, a profound diuresis. Even when Frank, in 1912, first brought to notice the striking connection between the condition of diabetes insipidus, in man, and interference with the pituitary posterior lobe by disease, or by mechanical injury, he was inclined to attribute the effect to irritation of the lobe, causing an excess, rather than a defect, of its endocrine activity. Such an interpretation, however, became clearly inapplicable, when in the following year, 1913, two independent observers, von den Velden and Farini, both described the successful use of injections of the posterior lobe extract for the treatment of diabetes insipidus; for if the fault in that condition had been due, as suggested, to an excessive output of a diuretic hormone by the lobe, giving more of it, by injecting the extract, should surely have made the condition worse. In any case, it was soon clear that, however they acted, suitable injections of the extract, given hypodermically at appropriate intervals, would render the kidney function of the sufferer from a typical diabetes insipidus practically normal; he no longer passed great volumes of dilute urine, and no longer needed to drink great quantities of water to replace what would thus have been lost.

Taken by itself, this remarkable therapeutic action might clearly have suggested that the real, physiological function of the pituitary posterior lobe was to produce, not a diuretic hormone, as Schäfer's experiments with Magnus and with Herring had seemed to suggest, but an antidiuretic hormone, in the absence or deficiency of which water and salts, from the blood, would be allowed just to run through the kidney as through a filter, and thus to produce the condition seen in diabetes insipidus. And that is, indeed, the conception which the later evidence has fully supported; but science had to wait for that till after the first world war, the outbreak of which was so soon to turn men's minds to other and what seemed to be more immediately urgent matters.

Before we pass, however, to this later evidence, it may be of interest to the members of your Diabetes Association, and especially to those who are interested in the treatment not only of the much commoner diabetes mellitus, but also of the relatively rare diabetes insipidus, to recall that the specific treatment of the latter, by correction of the pituitary hormone deficiency which caused it, was successfully introduced some nine years before insulin became available for the treatment of diabetes mellitus. The pituitary posterior lobe hormones being stable to boiling in water, the project of preparing an active and sterile extract containing them had encountered no such difficulty as that which, for so many years, had frustrated all attempts to extract insulin from the pancreas. And, indeed, such active pituitary posterior lobe extracts, equally suitable for treating diabetes insipidus, had, by 1913, been already for some four years in general use in obstetrics. For one reason or another, then, the discovery of this specific treatment, for the relatively rare and much less serious diabetes insipidus, attracted but

little general attention; and we had to wait till the years between the two wars for the elucidation of its rational, scientific basis.

From the large array of evidence which eventually provided this, I can again select only what seem to me to have been outstanding items. It can be taken as now generally accepted, I suppose, that the formation of normal urine by the kidney involves two main stages—the production in initially large volume of a dilute fluid which is, essentially, a glomerular ultrafiltrate from the blood, and then the concentration of this in the tubular part of the kidney, by the reabsorption of much of the water and the addition of other constituents. In typical cases of diabetes insipidus it was essentially the reabsorption of water which was defective; and this appeared to be restored by injecting the postpituitary extract. Starling and Verney were able to show, indeed, that when an isolated kidney of a dog was perfused with blood from a system containing only the heart and lungs, it soon began to excrete a voluminous, dilute urine, like that of diabetes insipidus; but that the addition of a small dose of the postpituitary extract to the circulating blood caused the kidney promptly to produce a much smaller volume of normally concentrated urine. Then Verney was able to show that the same remedial, normalizing effect, on the function of such an isolated kidney, could be obtained by including the dog's head, as well as the heart and lungs, in the artificial circulation; but that this was no longer effective if the pituitary body was removed from the perfused head. And Verney was then able to carry the demonstration further, under more strictly physiological conditions, on practically normal, conscious dogs, and to show that the volume and the concentration of the urine, which these excreted after drinking water, were subject to a control, retarding the rate and increasing the concentration, by the output of an antidiuretic hormone from the pituitary posterior lobe, which could be excited by emotional stimuli, or by inducing a sudden, small increase of the salt concentration of the blood in the carotid artery, on its way to the head—a signal for the need of more water in the blood, evoking the appropriate hormonal response.

I mentioned the fact that earlier observations of the effects of removing the posterior, neural pituitary lobe had given ambiguous and conflicting results. Here again the more recent evidence appears to have clarified the situation. An important investigation by Ranson, Fisher and Ingram, using methods which more exactly localized the structures divided or extirpated, seems to have made it clear, at last, that a substantially complete removal, or a degeneration, of the pituitary posterior lobe, with its stalk and infundibular attachment, regularly produces a diabetes insipidus in the cat, or the monkey. And several other observers, who have made separate extracts from the pars intermedia and pars posterior of the pituitary bodies, from a number of species in which those parts are themselves completely separate, have been able to confirm the fact that it is from the posterior lobe alone, the pars nervosa and the stalk which connects it to the brain, that extracts are obtained which show the characteristic, antidiuretic, pressor and uterus-stimulating activities, which have now so long been known.

## NEURAL CONTROL OF HORMONE PRODUCTION

I mentioned experiments in which the mere division of certain structures related to the pituitary posterior lobe, without surgical extirpation of any part, produced a diabetes mellitus in the animals on which such operations were performed. These, in particular, were operations which separated the lobe from all connections with the groups of nerve cells in the midbrain, in which the fibres of the rich nerve-supply to the lobe have their origin. During recent years there has been a steady flow of intensely interesting publications, recording and discussing the results of anatomical and experimental observations, which have a most important bearing upon the meaning of these phenomena. Again I can do no more than make an arbitrary selection, for briefest summary. Of central interest for our purpose is the evidence that the neurohypophysis, the posterior neural, pituitary lobe and its stalk—unique, it would appear, in this respect among all the ductless glands—is completely dependent for its endocrine function on the integrity of its abundant nerve-supply. When the stalk transmitting this nerve supply is divided, or when the nerve-fibres are otherwise cut off from their cells of origin in the brain—cells of the supra-optic and paraventricular nuclei—not only do these fibres degenerate, but, with them, so much of the posterior lobe itself degenerates, that it not merely ceases to *secrete* its hormones into the blood, in response to the normal, physiological stimuli; it fails even to *form* them, so that they can no longer be obtained from the lobe by artificial extraction. Other cases of endocrine organs have long been known, indeed, such as that of the suprarenal medulla, in which the rate of output of a hormone is greatly influenced by reflex stimulation, reaching the endocrine cells through their nerve-supply. In such cases, however, it is only the secretion, not the formation of the hormone which is under such nervous control. Section of the splanchnic nerve-supply to the

suprarenal medulla leads to an accumulation of epinephrine in its cells, rather than to its disappearance. The physiological connection between the endocrine structures in the pituitary posterior lobe, the nerve fibres reaching it from the brain and forming so large a component of its substance, and the nerve cells in which those fibres originate, appears, on the other hand, to be of a different and a peculiarly intimate nature. I have mentioned the fact that the histology of the lobe, as seen in man and most animals, is such as to suggest a nervous, rather than a secretory function. A clearer picture, of the structures in it responsible for the hormone formation, appears to have been obtained by a study of the organ from more primitive animal types. Bodian has recently given a remarkable description of the structure of the pituitary posterior lobe of an opossum. This exhibits, in section, special elements arranged in a "palisade" form round the peripheries of the lobules, into which, in that species, the lobe is clearly divided. A nerve fibre ends in each such element, which appears, indeed, to have no independent cellular existence, but to form a kind of sheath round the nerve-fibre ending. A special staining-reaction, indeed, which the author is inclined to attribute to the actual hormones, or, perhaps, to a substance containing them, is not only exhibited by these terminal, palisade-like structures, but can also be traced back along the nerve fibres to their cells of origin in the brain, on which a covering of the substance giving this distinctive staining reaction can still be observed; and the suggestion naturally arises that the cells of these hypothalamic nuclei are not merely concerned with a nervous control, in the ordinary sense, of the production and internal secretion of the post-pituitary hormones, but are actually components of a continuous structure responsible for their production—a suggestion which is highly original and seemingly without precedent, in relation to any other known endocrine structures in mammals, or, indeed, in other vertebrates; though there are certain neuro-glandular structures in insects, which appear to offer some kind of analogy. And we may find, perhaps, a more distant analogy, in the observation that the now well-known chemical transmitters of the effects of nerve impulses are stored, not only at the nerve endings from which they are released for action, but, in smaller concentration, along the whole of the nerve fibres concerned; and in the fact that these transmitters likewise disappear rapidly from the nerve-endings, where they are normally stored for release by nerve impulses, and from the nerve fibres to which the endings belong, if the connection of these fibres with their nerve-cells of origin is broken by section. This matter may appear, however, to have too great a physiological importance to permit of its discussion merely on a basis of analogies, which may be misleading. We must wait, but wait eagerly, for more direct evidence to justify such a comparison between the neuro-hormonal function of the pituitary posterior lobe, with its connection with the hypothalamic nuclei, and the now generally recognized neuro-humoral transmitter function at nervous synapses.

## CHEMICAL NATURE OF POSTERIOR PITUITARY HORMONES

Meanwhile there is another intensely interesting and still more recent development, dealing with the chemical nature of these hormones of the pituitary posterior lobe. I have said that, at one stage, I myself had thought it reasonable to assume that the different activities of the extract, on the arteries, the uterus and the kidney function, might all be due to the same active substance, in default of evidence to show that more than one was concerned. Later, however, my own biochemical colleague, the late H. W. Dudley, appeared to me to have produced decisive evidence of this kind, by obtaining the oxytocic activity free from the pressor activity, and the pressor activity with only a minor remnant of oxytocic activity, in separate solutions, as the result of a simple, physical, solvent partition between butyl-alcohol and acidulated water. Professor Abel did not agree with us; but the question seemed to me to be settled in our favor when Dr. Kamm and his colleagues, of Parke, Davis & Co.'s research laboratories, produced a similar separation by a method suitable for large scale working, so that two solutions, each with one only of these types of activity, were made available for therapeutic uses. And it should be noted that, with any separation which had thus been effected, the antidiuretic activity always went with the pressor, and none of it, apparently, with the oxytocic fraction, but that no pressor-antidiuretic fraction was ever obtained which did not exhibit also a minor degree of oxytocic activity.

In years more recent, and in a series of brilliant researches which are still in progress, Professor DuVigneaud and his team of associates have obtained results which have raised our knowledge of the active constituents of this pituitary extract to an entirely different level—to a height of achievement, indeed, which I had certainly not expected to be reached during my lifetime. The active constituents had long been known to be relatively stable substances, indeed; but they were so intensely active, that extremely minute quantities of them

would account for the effects of large volumes, even, of active extract. Yet, by the use of modern methods of separation, by counter-current distribution and chromatography, DuVigneaud and his team have now separated the oxytocic and pressor-diuretic hormones from the extract, both in such purity as to have made it possible, in each case, to identify the eight different amino-acids, which are united by amide linkages to form the two different cyclic-polypeptide molecules of the two hormones. In the case of the oxytocic hormone they have even been able to verify the remarkable structure thus deduced, by making it artificially by synthesis, and confirming the complete identity of the artificial with the natural product, in physiological activity as in every other character. And, if they have not done so already, I should be willing to wager that they will very soon have produced the pressor-antidiuretic hormone also, in pure form, by artifiical synthesis. They have already discovered, indeed, that the pressor differs from the oxytocic molecule in respect of two only of the eight constituent amino-acids; and they have even demonstrated that the molecule of the pressor hormone from the pig's pituitary gland differs from that obtained from the ox, by the substitution in it of lysine for arginine. All the available evidence seems to indicate, further, that the pressor and the antidiuretic hormone are, indeed, one and the same substance, and that this does, even when pure, possess a minor stimulating action of its own upon the uterus. The main oxytocic hormone on its part, free from any pressor action, appears to be entirely responsible for another effect of the extract, which I have not mentioned yet, namely, an action upon the active mammary gland, causing a propulsion of the milk, in preparation for its discharge from the nipple—a function which, as naturally brought into action, has even a notable importance of a practical kind, in connection with the response of dairy cows to milking.

And there is another direction, in which this galactogogic action of the oxytocic principle of the extract seems to offer evidence of interest concerning the endocrine functions of the posterior pituitary lobe. I have mentioned the argument, in which Dudley and I found ourselves involved with the late Professor Abel, on the question whether the extract contained one, or more than one, specifically active substance. I think that the question with which we, on our side, were alone concerned, namely, whether more than one substance is concerned in the action of the artificial, boiled extract, has been answered more definitely and emphatically than ever, by this beautiful work of DuVigneaud and his team. Nobody, I think, can longer doubt that such an extract contains two active constituents—the pressor-antidiuretic and the oxytocic-galactogogic. Professor Abel, however, concerned himself at a later stage with a different question, which we had not attempted to touch, namely whether the hormones are naturally present as separate constituents of the living gland substance, or, as he was disposed to maintain, as side-chains or prosthetic groups attached to the same macromolecules. In support of such a view, Professor Van Dyke has, in fact, more recently obtained evidence of the presence, in a juice expressed from the fresh posterior-lobe substance, of a protein which moves like a single chemical entity in an electric field, but appears to possess both the two activities, in the same proportion to one another as that with which they appear in the boiled extract. I myself was the less inclined, however, to draw definite conclusions from such an observation, on account of earlier experiences, with two different chemical colleagues, at an interval of a good many years, from both of which it appeared that even crystalline picrates and picrolonates of inert, organic materials, might carry down with them, out of solution, the two forms of activity from the ordinary extract, in their original proportion. The important matter from the physiological point of view, I think, is in any case to know, not whether the two active substances are somehow associated with a common protein basis in the gland, but whether they leave it as separate hormones, or together as one, at the call of the different physiological needs for their actions. And the most suggestive observation in that direction, so far, is the recent finding that the posterior lobe of the female mammal in lactation becomes, apparently, largely depleted of its oxytocic-galactogogic hormone, while retaining its normal load of the pressor-antidiuretic one. There is, of course, nothing yet to exclude the possibility of their being attached to a common macromolecule in the lobe, provided that a physiological mechanism exists for their separate release from such an attachment.

## DEVELOPMENTS IN THE FUTURE

Having watched the investigation of the activities of the pituitary posterior lobe practically from its beginning, with Oliver and Schäfer's first description of its pressor action, I experience a thrill of excitement and a peculiar sense of satisfaction, in seeing the rapid recent emergence of knowledge, so clear and decisive, concerning the chemical nature of the extremely active hormones which it produces. We are becoming accustomed to such thrills, however, in these days of headlong scientific progress; and

I think that we may allow ourselves to ask on this commemorative occasion, whether there is any likelihood that it may yet become possible to produce insulin also by an artificial synthesis, and thus to remove any cause for anxiety about a possible world-shortage of pancreas for its manufacture. I could not venture to prophesy with any confidence; on the other hand, as I grow older, and watch the conquest, one after another, of scientific objectives which many of us had earlier abandoned as impregnable, I find it ever more difficult to restrain my optimism. Perhaps, indeed, we are entitled to find some more direct encouragement here in Professor DuVigneaud's own statement, concerning the manner in which he and his team came to work on the pituitary hormones. "Our interest," he tells us, "in the hormones of the posterior lobe of the pituitary gland, grew out of the work which we did on the chemistry of insulin."

One feels disposed to hope that, with the aid of the further light already thrown on the polypeptide structure of insulin by the work of Sanger and others, they may yet be encouraged to return to it, by their own successful attack on the chemistry of the pituitary posterior-lobe hormones; or that some other team may seize the widening opportunity which modern biophysical and biochemical methods so enticingly present.

In one way or another, I am constrained to believe, at least to entertain a hope, that insulin, too, may yet be synthesized.

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## *The Rôle of the Internist*

To understand the rôle of the physician in any age is to understand the culture of that period. For he more than any other in all stages of our painful progress from savagery to civilization epitomized his times. When a culture developed and bloomed, the physicians rose with it, in fact often led and vitalized the movement, and the decay of great civilizations is more accurately measured by the degradation of the healing art than by any other yardstick. His rôle reflected in a most profound way the beliefs, the knowledge and the morals of the times and changed as these mores changed. In tune with his times he has been priest, simple craftsman, philosopher, biologist and now must be perforce social scientist.

The complexity of modern medicine requires the internist more and more frequently to assume these three important functions: first that of co-ordination, second that of integration, and third that of interpretation.

For the patient the exercise of these functions means that the internist becomes the guide for his patient through the medical maze in which he might well be lost. He integrates the factors of heredity and environment, of nutrition and emotional stress, and of all past and present systemic disorders, together with the personality of his patient. He becomes in short the personal physician. And this ancient rôle, so precious in our past, is even more needed in these days. The internist almost alone among the many specialists has—or he should have—the aptitudes necessary to become the personal physician. Of course among these aptitudes perhaps the most important is diagnostic acumen in the widest sense. This encompasses not only the ability to name the specific disease from which the patient suffers but the ability as well to understand and evaluate all the factors in the patient's situation which will affect his reaction to the disease. This involves in a personal, but for the patient a vital way, the exercise of the three functions we have described. The internist brings together all the factors which bear on the problem at hand, which is integration; he co-ordinates the findings of his colleagues with his own observations; and he interprets these things to the patient both by what he says and by his therapy.

The desirability of integration and co-ordination within the profession is too obvious to require comment, and in this group I think that it would be agreed that the internist is the one to do the job. We must assume more responsibility for the integration of our already dangerously fragmented profession. The rôle of the internist is like that of the conductor of a symphony orchestra. It is for him to see that harmony and not discord results from the co-ordinated activities of the individual performers—including the prima donnas, if such there be in the case. There is an added and often neglected obligation to our fellows to see that due credit and recognition are given to those who deserve it. Many an internist smugly takes the credit for a brilliant diagnosis which was in fact made not by him but by some completely anonymous roentgenologist or clinical pathologist. We must of course be ready to help our fellow practitioners but we must also be ready to accept help when we need it and to give credit to our helpers. The internist must not arrogate to himself arbitrary controls but must in all humility accept his rôle within the profession.

These then are the rôles of the internist: for the patient, a councilor and guide; for the profession, an integrator and co-ordinator; for society, a liaison agent, interpreter and leader.

Russel V. Lee, M.D., in the *Annals of Internal Medicine,* October 1953.

# Insulin Extractable from the Pancreas and Islet Cell Histology

## Comparative Studies in Spontaneous Diabetes in Dogs and Human Subjects

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*Charles H. Best, M.D., D.Sc.,‡ Toronto*

The characteristics of diabetes mellitus in man have long been compared, either directly or by inference, with those of diabetes produced in animals by experimental means. From the earliest studies in this field by von Mering and Minkowski,[1] in the work leading to the discovery of insulin[2] (1921), and in many later investigations, the dog has occupied a prominent and productive place amongst experimental animals. In recent years, special aspects of the spontaneous diabetes of dogs have come under study in this laboratory and in that of Professor Henry Ricketts in Chicago.

It is the purpose of this paper to examine the available data to determine the degree to which the spontaneous and the experimentally induced diabetes mellitus of dogs correspond with each other and with the spontaneous diabetes mellitus of man, in terms of the insulin extractable from the pancreas and the histological state of the islands of Langerhans. The relationship of these factors to the diabetic state with which they are associated will also be considered.

From the Banting and Best Department of Medical Research, University of Toronto, Canada.

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### MATERIALS AND METHODS

To the best of our knowledge, measurement of the insulin of the pancreas from dogs with spontaneous diabetes is currently limited to eleven cases. Four pancreases from such diabetic dogs were extracted and assayed by us for Dr. Ricketts, while the remaining seven represent subjects from our own series which have come to autopsy. These were obtained through interested veterinarians and medical men during the past seven years. In four cases the owners did not wish to retain the diabetic dogs as pets. These were killed by intravenous nembutal at the owners' request following periods of laboratory study of eight, ten, twenty-one, and thirty-eight days, respectively.

In another four cases the dogs were returned to their owners with typed instruction sheets following initial two-week periods of adjustment to a measured diet and protamine-zinc insulin. Arrangements were made to readjust diet and insulin dosage for these animals every three months, with autopsy to be held at the laboratory in case of death. While this course of events entails certain experimental hazards, it was adopted since it approximates that to which many diabetic subjects are exposed, and thus establishes a closer parallel between the courses of the spontaneous diabetes of dogs and of man. Data on the insulin of the human pancreas, with which corresponding values for diabetic dogs are compared, have been collected concurrently with those for the diabetic dogs.

The acid alcohol method of Scott and Fisher[3] was used for the extraction of insulin from the pancreas for both the human and canine subjects. Estimations of the insulin concentration in such extracts were made, using

a mouse convulsion method of assay, meeting the requirements recommended by Bliss[4] for this type of assay.

Sections from the body of each pancreas were taken for histology. These were placed in Bouin's fixative for twelve to sixteen hours. A variety of staining procedures was applied, but those of greatest importance in the present study were Gomori's[4] hematoxylin and phloxine, and Wilson's[6] modification of his aldehyde and fuchsin, which stains beta cell granules a deep purple against a pale green background. An example of glycogenic vacuolation of cells in pancreatic ducts is shown in figure 1 (dog-SU).

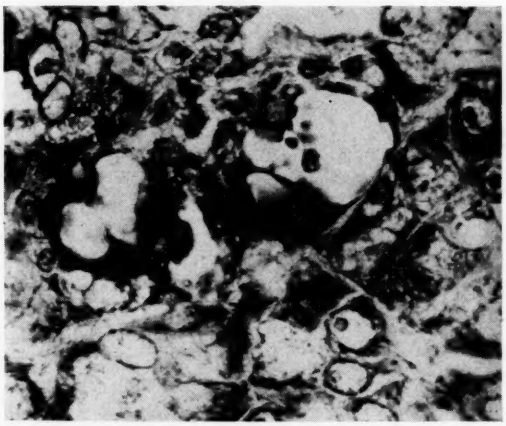


FIG. 1. Ducts in the pancreas of dog SU contain stainable deposits of glycogen, which appears black, above. Best's carmine stain; paraffin section; X 800.

Complete autopsies were performed on all animals, and blocks both for paraffin and frozen sectioning were taken from kidneys, livers, and hearts, and only for paraffin sections from the thyroid, adrenal, pituitary, gonads, and spleen. Frozen sections were stained by Wilson's modification of Lillie's supersaturated Isopropynol Oil Red O technic. Paraffin sections were stained with hematoxylin and eosin and by a variety of methods to demonstrate selected tissues.

## RESULTS

Characteristics of the eight dogs of the present series with spontaneous diabetes mellitus are included in table 1. Of these only two were male. One female and one male dog were spayed as pups. The seven of these eight dogs which have come to autopsy varied in age at death between 5.2 and 9.6 years (average 7.7 years). The surviving dog, while mature, is by far the youngest member of the series (3.1 years).

The development of diabetes was preceded by overweight in at least four out of eight of the cases, and was followed by marked weight loss in all cases. In two of the obese dogs, the pancreatic duct was blocked at autopsy and the pancreas had become reduced to a fibrotic remnant. In the other four, the pancreases did not appear abnormal in size or texture, except that in one dog (D-WA) there was fatty degeneration. An active thyroid tumor weighing 86 gm. was removed surgically from the neck of one of the two male dogs of the series (D-CO); following its removal, the severity of the diabetes was decreased. The relationship, if any, of these factors to the etiology of the diabetes remains inferential at the present time.

Fasting blood sugar concentrations before start of diet and insulin therapy varied between 130 and 346 mg. per 100 cc. The lowest of these values was observed in a bitch (D-LA) which showed a negative test for urinary ketone bodies on admission, and which later required nearly three times as much insulin to control the diabetes. At autopsy, no islet cells could be found in the histologic sections of pancreas for this animal. Except for the negative tests obtained for this dog shortly after diagnosis of the diabetes, urine samples from all of the spontaneously diabetic dogs were positive for ketone bodies when insulin therapy was discontinued for two days. Bornstein and Lawrence[7] have reported that ketosis in diabetic human subjects occurs in association with low levels of blood insulin.

Observations on the insulin extractable from pancreas and the abundance and granulation in the beta cells of the islets of Langerhans for the spontaneously diabetic dogs are shown in table 2a, together with the histologic observations on four dogs reported by Ricketts and his associates.[8]

With the exception of three dogs which were autopsied within one month of the diagnosis of diabetes, few or no beta cells were found in the histologic section of the pancreas and, where found, the abundance of beta cell granulation was very low. Correspondingly, all values for the extractable insulin of the pancreas in dogs autopsied after the one-month interval were extremely low, as indeed were the values in most of those which were autopsied before this time.

A comparable situation was found to exist when a similar chart of extractable insulin and beta cell histology was drawn up for fourteen human subjects whose diabetes had been diagnosed during the normal period of body growth (roughly the first two decades of life). Here again the islets of Langerhans of some of the

TABLE 1

Characteristics of dogs with spontaneous diabetes mellitus

| | D-WA | D-CO | D-JU | D-SU | D-LA | D-BO | D-MI | D-DA |
|---|---|---|---|---|---|---|---|---|
| *General* | | | | | | | | |
| Sex | M (spayed) | M | F | F (spayed) | F | F | F | F |
| Breed | Spitz-Pomeranian | Spaniel | Mongrel | Wire-haired Terrier | Irish Setter | Wire-haired Terrier | Mongrel | Greyhound |
| Nose to rump distance (cm.) | 65 | 74 | 60 | 63 | 103 | 63 | 69 | 96 |
| *At admission* | | | | | | | | |
| Blood sugar (mg. per 100 cc.) | 300 | – | 183 | 340 | 130 | 175 | 192 | 238 |
| Urine sugar | (positive) | 5% | 1% | 2% | 4% | 0.2% | 5% | 5% |
| Ketonuria | (positive) | – | 4+ | 3+ | Trace | 0 | 4+ | 4+ |
| *During diabetes therapy* | | | | | | | | |
| P.Z. insulin (u/day/kg.) | 1.3 | 1.5 | 2.1 | 2.0 | 0.5 later 1.3 | 2.9 | 2.7 | 1.1 |
| Duration (months) | 3 | 18 | 1.3 | 1.7 | 4.8 | 13 | 0.8 | 1.2 |
| *At death* | | | | | | | | |
| Bilateral cataracts | 0 | 4+ | 2+ | 0 | 1+ | 0 | 2+ | 4+ |
| Condition at death | Diabetic coma | Intussusception | Killed | Killed | Vaginal infection, pneumonia | Living | Killed | Killed |
| Age (years) | 6.5 | 8.5 | (9) | 5.2 | 8.3 | 3.3 | 7 | 9.6 |
| Body weight (kg.) | 8.8 | 13.6 | 6.7 | 10.8 | 22.5 | 6.8 | 10.4 | 22.9 |
| Pancreas wt. (gm.) | 25 (fatty) | 20 | 27 | 4.8 | 47 | ( ) | 10 | 88.3 |
| *Extractable insulin* | | | | | | | | |
| Units/kg. body wt. | 0.14 | 0.16* | 0.35 | 0.09 | 0.16 | Living | Under 0.06 | 0.25 |
| % of nondiabetic av. | 2.9 | 3.4 | 7.3 | 1.9 | 3.4 | – | Under 1.3 | 5.2 |

*Biopsy.

subjects with newly diagnosed diabetes mellitus were found to have appreciable numbers of beta cells but with scant and poorly granulated cytoplasm. In none of those subjects whose diabetes had been diagnosed for more than a year were the extractable insulin, number of beta cells, or abundance of beta cell granulation found to be above trace levels (table 2b).

In human subjects with diabetes of the growth-onset type, as well as in the spontaneously diabetic dogs of our series, depletion of beta cells appears to precede loss of alpha cells to some degree, but eventually both types of cells may become so scarce that it is difficult to locate and identify any islet cells in histologic sections of pancreas from such long-term diabetic subjects.

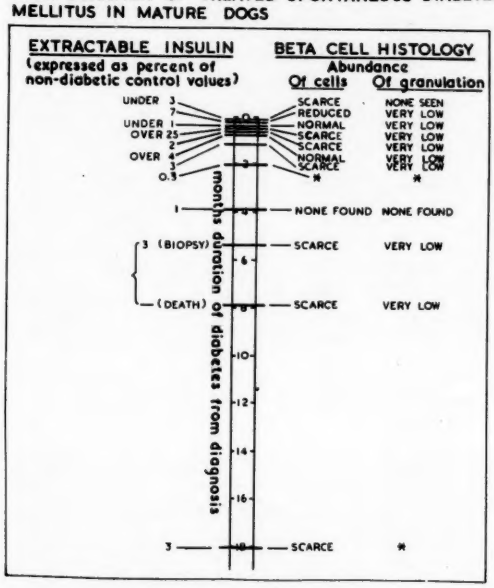
Lesions in organs other than the pancreas encountered at autopsy are summarized for all seven dogs in table 3. Only brief mention of findings of special interest will be made here. In dog JU, frozen sections of the kidneys presented a striking picture. The glomerular capsules, as well as the spaces of Bowman within the glomeruli, were filled with masses of stainable fat (figure 2). In a few glomeruli fat could be seen within the lumina of the glomerular capillaries. The basement membranes of the proximal convoluted tubules in this dog's kidneys were coated with intensely sudanophilic fat. The fat had precipitated on the fibrils of the tubular basement membrane (figure 3).

The kidneys of dog SU were perhaps of even more interest than were the kidneys of the preceding animal, The glomeruli of these kidneys exhibited lesions which closely simulated those of intercapillary diabetic glomerulosclerosis in an early stage. Focal lesions were observed in a small percentage of the glomeruli (figure 4). (A normal canine glomerulus for comparison is shown in figure 5.) In frozen sections of this kidney, lipid plugs could be demonstrated within the glomerular capillaries in the regions of these lesions.

Stainable fat was present in the tubules of nearly all

TABLE 2a

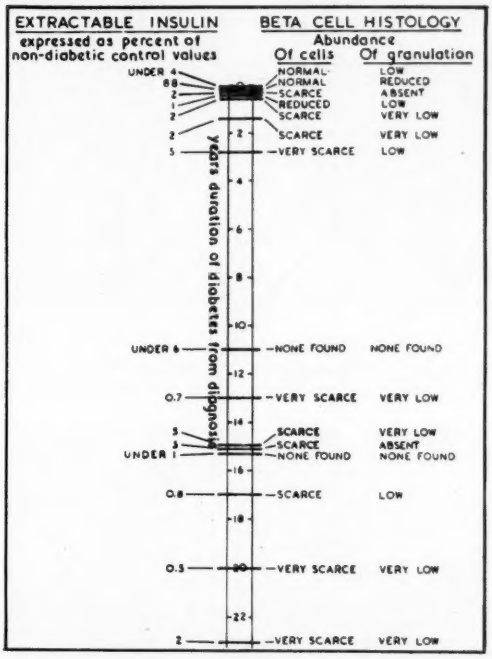
EXTRACTABLE INSULIN OF PANCREAS AND ISLET BETA CELL FREQUENCY AND GRANULATION COMPARED WITH DURATION OF TREATED SPONTANEOUS DIABETES MELLITUS IN MATURE DOGS




* unobservable due to postmortem change

TABLE 2b

EXTRACTABLE INSULIN OF PANCREAS AND ISLET BETA CELL FREQUENCY AND GRANULATION COMPARED WITH DURATION OF TREATED GROWTH-ONSET DIABETES MELLITUS IN MAN



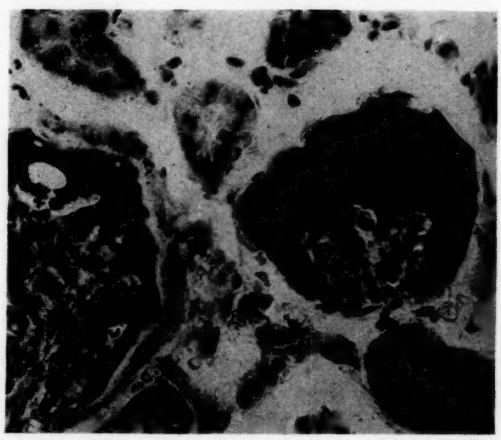



FIG. 2. Masses of sudanophilic lipid (black) fill Bowman's spaces in many of the glomeruli of frozen sections of the kidney of dog JU, shown above. Oil red O stain; X 600.

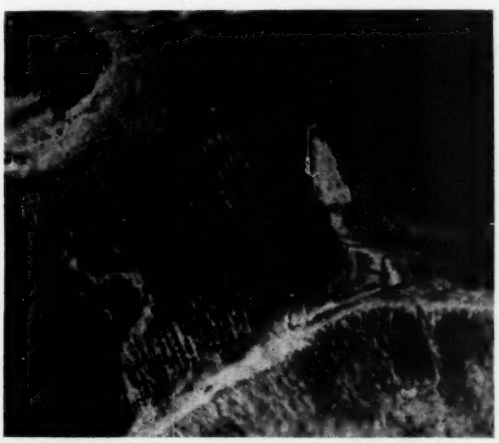


FIG. 3. The basement membrane of a portion of a proximal convoluted tubule is shown in tangential section in a frozen section of the kidney of dog JU. Stainable fat has precipitated on the membrane fibrils, making them stand out sharply in black in the photograph. Oil red O preparation; X 800.

kidneys examined in the series with the exception of dog DAV and dog MI. The fat was confined in most instances to the cells in the walls of the descending portions of the cortical tubules. In two animals, however,

TABLE 3

Summary of histologic findings in the tissues of spontaneously diabetic dogs

| | D-CO | D-JU | D-SU | D-LA | D-DAV | D-MI |
|---|---|---|---|---|---|---|
| *Pancreas* | | | | | | |
| No. of islets | Very scarce | Not scarce | Very scarce | None found | Scarce | Very scarce, hyalinized |
| Beta cell granulation | Almost none | Almost none | Almost none | None | Almost none | None |
| Beta and duct cell hydropic (glycogen) vacuolation | Present | Present | Present | – | Present | – |
| Fat | Fatty | Normal | Normal | Normal | Normal | Fibrosis++ |
| *Kidneys* | | | | | | |
| Glomerular | Many fat droplets | Capsular and capillary loop fat | Capsular and capillary loop fat, glomerulosclerosis | Normal except for fat | Capsule thickening; fat in capsular space | Fat emboli, early glomerulosclerosis |
| Tubular fat | Present in both loops | Present in distal loop only | Present in distal loop | Normal except for fat | Little | Normal |
| *Liver* | | | | | | |
| Fat | Marked fat vacuolation, early nonportal fibrosis | Severe centrolobular fatty change | Slight to moderate centrolobular liver fat | Uniformly distributed fat, centrolobular congestion | Normal (little fat) | Centrolobular fat, fatty cysts |
| Glycogen | Abundant | Normal | Normal | Normal | – | Normal |
| *Heart* | Normal | Normal | Normal | Fatty degeneration and necrosis | Fat infiltration, coronary artery thickening | Coronary artery narrowing |
| *Thyroid* | Absent | Normal | Normal | Normal | Normal | Normal |
| *Adrenals* | Normal | Normal | Normal | Normal | Normal | Normal |
| *Pituitary body* | Normal | Eosinophils prominent | Eosinophils prominent | Normal | Eosinophils prominent | Normal (calcification) |
| *Arteries* | Normal | Normal | Normal | Normal | Normal | Aortic, coronary, pancreatic, and renal arteriosclerosis |
| *Spleen* | Normal | Normal | Normal | Normal | Normal | Normal |

D-CO and D-LA, stainable fat was present not only in these portions of the tubules, but also in the convoluted portions of the proximal loops (figure 6). Abnormal deposits of glycogen were not encountered in tubules of any of the kidneys of the dogs.

In four of the six animals abundant amounts of fat had accumulated in their livers, and in one of the remaining two animals there was a slight trace of liver fat. In every instance in which stainable fat was present in the animals' livers, the distribution of the lipid was centrolobular or nonportal. In one animal only D-CO, early fibrosis, as well as fat in nonportal regions of the liver, was encountered (figure 7). Hearts that were examined in this series were not remarkable, with the exception of dogs D-LA and D-DAV. In dog D-LA, fatty degeneration, necrosis, and calcification of heart muscle constituted prominent features (figure 8). Nearly every cardiac muscle fiber in this animal was swollen with stainable fat droplets. Scattered throughout were focal areas of cardiac necrosis in which inflammatory cell infiltration had occurred with lysis of muscle and calcification of the necrotic debris. The heart of dog D-DAV contained a small amount of stainable fat and a few focal areas of fibrosis, but lesions were not nearly so advanced or widespread as in dog D-LA (figure 9).

In only one animal, D-MI, were degenerative arterial

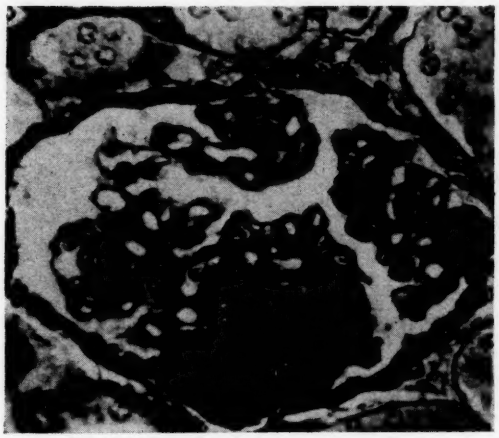


FIG. 4. A lesion which closely simulates diabetic glomerulosclerosis in man is shown above in a PAS-stained paraffin section of kidney from dog SU. Paraffin section; X 500.

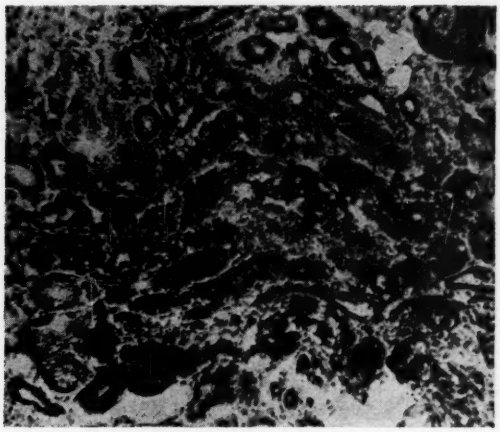


FIG. 6. Stainable fat (black) is present in many of the convoluted portions of the proximal segments of the tubules in this frozen section of kidney from dog CO. Oil red O stain; X 300.

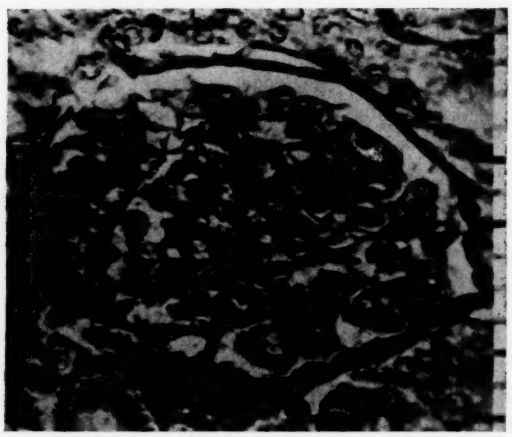


FIG. 5. Normal glomerulus of dog in a section stained in the same manner as shown in figure 4. Compare the thickness of the basement membranes (black) in this photograph with those shown in figure 4; X 500.

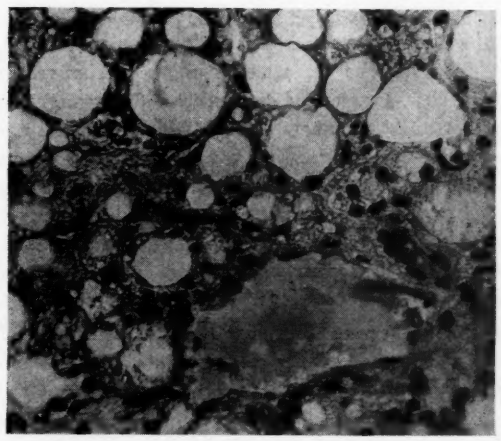


FIG. 7. Fat vacuolation and some early fibrosis (lower right) are present in this paraffin section of the liver of dog CO. Much of the fat is contained within cysts of the type seen in the livers of choline-deficient rats. Hematoxylin and eosin stain; X 400.

lesions demonstrated. In this dog, lesions identical with those seen in human atheroma were encountered in the aorta, in the coronary arteries, in the renal vessels, and in the pancreatic arteries. These lesions consisted of subintimal and intimal thickening with deposits of fat and cholesterol in the affected portions. The underlying media had frequently undergone degeneration, fibrosis, and focal areas of calcification. In every site, these changes were indistinguishable from those of atheromatous degeneration in comparable arteries of man.

Although this series of animals does not include examination of a comparable number of control dogs that had experienced environmental conditions similar to those of the diabetic animals, nevertheless the occurrence of lesions in the kidney of one animal that resembled diabetic glomerulosclerosis in man and the presence of advanced atheromatous change in the arteries of another dog are of considerable interest. Similar glomerular lesions were seen in one of the four dogs studied by Ricketts and his associates,[7] but these authors did not encounter true atheroma. Stainable fat plugs obstructing flow of blood through glomerular capillaries

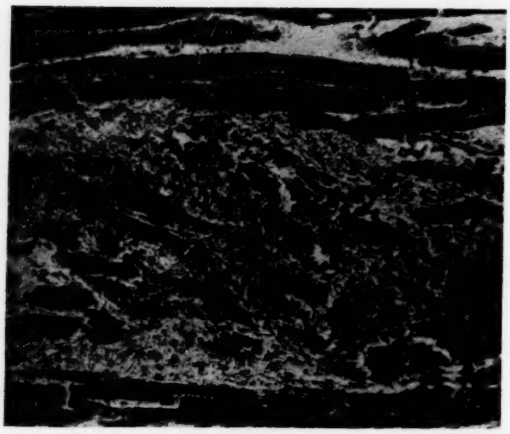


FIG. 8. Every muscle fiber contains droplets of stainable fat (black) in this frozen section of heart, stained with Oil red O, dog LA. The center of the field is occupied by fragments of necrotic muscle, inflammatory cells, and deposits of calcium.

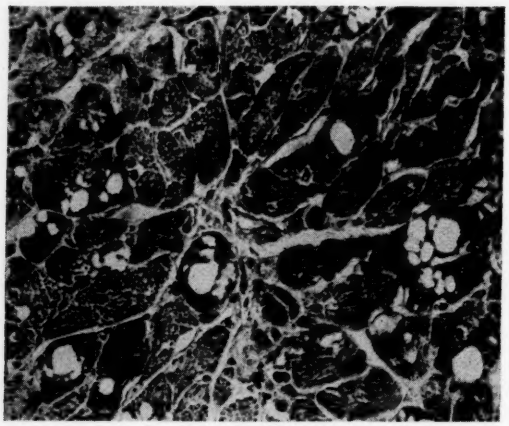


FIG. 9. Fat vacuoles occupy and distend muscle fibers in this paraffin section of heart from dog DAV. There is little fibrosis in the center of the field. Hematoxylin and eosin stain; X 400.

in dog SU suggests that the pathogenesis of this type of lesion may be the same as we have observed in choline-deficient rats and diabetic man (Hartroft[9]). We have described the stages through which glomeruli pass in choline-deficient rats in the development of lesions that closely simulate glomerulosclerosis in diabetic man. The lesions in the rat were initiated by lipid plugs in the glomerular vessels. Lipid plugs of a similar nature were found in 75 per cent of diabetic patients with Kimmelstiel-Wilson lesions. The evidence provided by the sections of kidney of dog SU suggests that the focal glomerular changes in this animal may have a similar pathogenesis.

The most consistent finding throughout the entire series in organs other than the pancreas was deposition of stainable fat in a variety of organs including the liver, heart, and kidney. It may be significant that deposition of abnormal amounts of fat in these organs and their sequelae (hepatic fibrosis, cardiac necrosis and fibrosis, intercapillary glomerulosclerosis) are all seen in varying degree in choline-deficient rats, spontaneously diabetic dogs, and diabetic man. Although choline deficiency in itself undoubtedly plays little role in either spontaneous canine or human diabetics, it is perhaps more than coincidence that similar lesions are seen in all three conditions. There is undoubtedly, common to all, a disturbance in the metabolism and transport of fat.

## DISCUSSION

The early progressive and profound loss of insulin-producing cells from the pancreas in the spontaneous diabetes of mature dogs and of human subjects with growth-onset diabetes reported here corresponds with other available published observations. Schlotthauer and Millar[10] and Ricketts and his associates[7] have surveyed the literature in English on the spontaneous diabetes of dogs, while Hjärre[11] has done so for German publications. In all papers, the close association between the presence of diabetes and degenerative changes in the islets of Langerhans is emphasized. In two of the cases reviewed, diabetic dogs were kept alive for a time before necropsy with diet and insulin. In one case islets were reported to be scarce and very small; in the other, none could be found.

The observed pattern of change with time in the extractable insulin of the pancreas and islet beta cell histology of the spontaneously diabetic dog parallels closely that described by Haist, Campbell and Best[12] following injection of a diabetogenic anterior pituitary extract in dogs. During the first few days of injection a reversible type of diabetes mellitus associated with degranulation of the islet beta cells and a profound fall in the extractable insulin of pancreas was observed. This condition was followed within a month or so by the disappearance of most or all of the beta cells, and the extractable insulin of the pancreas was then associated with a permanent or metadiabetic state. Since the islet beta cells regularly associated with insulin production are found to be absent from the pancreas in the permanent phases of experimental diabetes in the dog, it is rea-

sonable to conclude, as the above authors did, that the very low levels of extractable insulin of the pancreas regularly associated with them reflect a correspondingly low rate of production of endogenous insulin.

The validity of this interpretation is borne out by the experiments of Houssay and his associates, who demonstrated that the pancreases from dogs with either permanent pituitary diabetes (seven out of seven tested) or permanent alloxan diabetes (six of six tested) had lost most or all of their normal functional capacity to lower the blood sugar of the twenty- to forty-eight-hour depancreatized dog. The islets of Langerhans of such metadiabetic dogs were found to have effectively lost all beta cells when examined histologically 22-144 days after precipitation of the diabetic state (Houssay, Foglia, Smyth, Rietti and Houssay;[13] Houssay, Brignone, and Mazzocco[14]).

One of the most convincing pieces of evidence concerning the nature of growth-onset diabetes in human subjects was presented by Rao and Jackson.[15] Not only did they find that all of their series of forty-eight subjects required insulin to control their diabetes, but they found also that, within a year of its diagnosis, the amount of insulin required per day to maintain control and normal growth fell into a regular pattern, which increased with the age of the subject until the growth period was passed. This phenomenon would be observed if the endogenous supply of insulin in such subjects were negligible compared with their insulin requirement; that is, if they were "near-total" diabetics insofar as endogenous insulin supply is concerned. It also indicates that no pronounced dispersion in insulin requirement is caused in such subjects by endocrine factors other than insulin.

While the course of spontaneous and experimental diabetes in dogs appears comparable with that in the growth-onset type of diabetes of man insofar as the insulin and beta cells of the pancreas are concerned, it should be emphasized that the spontaneous canine diabetes occurred in *grown* animals in all but one of the seventy-one published cases of which we know.

In a majority of human subjects in whom diabetes mellitus was diagnosed following completion of skeletal growth (maturity-onset diabetes), the situation is quite different. Although the extractable insulin of the pancreas was found to be very low in some of these subjects, it amounts *on the average* to nearly 50 per cent of that found in the nondiabetic controls (Wrenshall, Bogoch and Ritchie[16]). This is more than twenty times as high as the average found in human subjects with growth-onset diabetes of more than one year's duration. The abundance of islet beta cell granulation, estimated from histologic sections independent of insulin assay values, is found to be correspondingly elevated in the maturity-onset diabetic subjects (Hartroft and Wrenshall[17, 18]). In sharp contrast to the disappearance, within one year of diagnosis, of almost all beta cells and extractable insulin from the pancreas of the human subject with growth-onset diabetes and the dog with spontaneous maturity-onset diabetes, little tendency for these factors to change with duration of diabetes was seen in the human subject with maturity-onset diabetes (Wrenshall, Bogoch, and Ritchie[16]).

The insulin of the pancreas and islet histology in the obese-hyperglycemic syndrome of mice (Mayer, Bates and Dickie[19]) is currently being investigated in relation to this group of diabetic human subjects.

## SUMMARY

In terms of the insulin of pancreas and the histology of the islet beta cells, the spontaneous diabetes mellitus of mature dogs and the diabetes of the growth-onset type in human subjects run parallel courses which correspond with that seen in the dog following the initiation of experimental diabetes by anterior pituitary extracts or by partial pancreatectomy.

This course is observed to be one of progressive and profound loss of beta cells and of the extractable insulin of the pancreas within relatively short times after onset of diabetes. It is in sharp contrast with the situation found in a majority of human subjects with maturity-onset diabetes, where pancreatic insulin and beta cell granulation are much more abundant and show little tendency to change with duration of the diabetes.

Lesions in organs other than the pancreas are briefly described and discussed, with emphasis on the kidney, heart and liver in the spontaneously diabetic dog.

## ACKNOWLEDGMENTS

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It is a pleasure to acknowledge the technical aid and skill of Mr. W. D. Wilson, both at autopsies and in the subsequent histochemical treatment of tissues, and of Misses Isabell Jasper and Patricia Dolan.

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## *A Prescription for the Aging and the Aged*

In the absence of fuller knowledge of the determinants of longevity, our efforts are chiefly to help an individual to achieve his expected life span in health, vigor and happiness. This calls not only for the prevention and cure of disease, but for the prescription of a proper mode of life for the aging as well as the aged.

This prescription has four ingredients: *Work, Rest, Diversion,* and *Moderation in all things.*

*Work* is the best way to preserve strength and function. The wheel that doesn't turn, rusts. Unused faculties and skills weaken and atrophy. Therefore "work" means the regular performance of physical and mental exercise and the doing of as many things as the individual knows how to do, as often as it is feasible to do them.

*Rest,* the second ingredient of our prescription, is needed in increasing amounts to prevent undue fatigue. The after-lunch siesta should be a regular part of the daily program of the elderly. Vacations should be longer in the yearly aggregate and are best divided into two or more segments during the year.

*Diversion* is at all ages an important means to health and happiness, but especially so during the increased leisure time of advancing years. But to do such diverting things well, they must be learned when we are young and must be practiced through the years. To grow old happily we must accumulate not only money in the bank but resources of the mind on which we can draw in old age. Therefore our early training and our education even at high school age should include some preparation for old age. Above all, we should be taught how to continue to educate ourselves by self-imposed studies that should begin when formal education is over and should continue as long as we live.

*Moderation in all things* applies not only to our work, rest and diversion, but such things as diet, habits and personal hygiene.

The most *useful therapeutic measure* in all aspects of treatment of the ills of the aged is *sympathy.* A kindly approach, a patient ear, a word of understanding of the oldster's problems, a cheerful word of reassurance and encouragement: These will potentiate the simplest remedies into miracle drugs; their lack will result in failure, because of the consequent absence of the greatest factor for the oldster's survival: the *will to live.*

Richard A. Kern, M.D., in the *Maryland State Medical Journal* 3:393-401, August 1954.

# Diabetes in Pregnancy

## Panel Discussion

*Garfield G. Duncan, M.D.**
*Philadelphia*
*Moderator*

*M. Edward Davis, M.D.†*
*Chicago*

*Lester J. Palmer, M.D.‡*
*Seattle*

*E. Stewart Taylor, M.D.§*
*Denver*

*Priscilla White, M.D.||*
*Boston*

MODERATOR DUNCAN: I should like to begin by asking Dr. Palmer to say a few words about the importance of the prepregnancy examination of the diabetic woman.

DR. PALMER: I have always felt that the diabetic woman in the childbearing age should not become pregnant by accident. I believe that we can gain that objective by proper education of these women as they learn more and more about the diabetic life. From the professional standpoint, there are definitely some diabetic women who should not become pregnant. If diabetic women do become pregnant, when pregnancy is contraindicated, then we are faced with the problem of deciding on therapeutic abortion or possibly, against our better judgment, being forced to permit the pregnancy to go on with the frequent result of a miscarriage or premature stillbirth. Further damage to the diabetes without accomplishing the desired results of a pregnancy may, and often does, occur. Therefore, we try to teach diabetic women that they should *electively* become pregnant; that they should use contraception until such time as they have consulted their doctors and found they are physically fit to become pregnant.

MODERATOR DUNCAN: I should like to ask Dr. White to comment on contraindications to pregnancy.

DR. WHITE: I have but one contraindication for pregnancy in diabetic women, and that is nitrogen retention or other evidence of renal failure.

MODERATOR DUNCAN: You would limit it to that, would you, Dr. White? Dr. Palmer, would you enlarge on that?

DR. PALMER: I think Dr. White is pretty liberal. I would certainly be alarmed about a patient becoming pregnant who I thought had evidence of even early, but rapidly progressive, retinitis. Certainly retinitis proliferans would be a contraindication from my point of view.

Dr. White may tell me that in a patient who has had long-standing kidney disease which contraindicates the pregnancy, that this contraindication is not infrequently independent of diabetes, and if that is what she means, I agree with her.

MODERATOR DUNCAN: You wouldn't then advise pregnancy in the case of a patient having advanced retinitis?

DR. PALMER: Advanced retinitis, no. I would advise against it.

MODERATOR DUNCAN: Will you comment on the retinitis feature, Dr. White?

DR. WHITE: We have advised against pregnancy when the patient had advanced retinitis, or retinitis until the current year. In 1950, Dr. Beetham pointed out that our fetal mortality was very high and that the retinopathies

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were progressing and not reversing following delivery. At that time we revised our therapy and increased the dosage of female sex hormones to what we consider the present maximum. Somewhat to our surprise, the fetal survival increased, and with this new schedule, the reports from Dr. Beetham are that the eyes are no worse at the end of pregnancy, and in some instances, an unprejudiced observer has said, they were actually somewhat improved.

MODERATOR DUNCAN: Those remarks make me feel a great deal better because within the past two years, I had a patient with retinitis who was especially anxious to have a family. I advocated going ahead. They did, and actually, her vision was improved during her pregnancy, and certainly has been no worse since she was delivered. This question of retinitis, I think, may bear re-evaluation.

Dr. Davis, will you discuss early induction of labor with pitocin and so forth, under favorable conditions, versus cesarean section?

DR. DAVIS: Patients who have made good progress during pregnancy with the diabetic state in good control, can be carried on to the end of pregnancy. We feel, however, as do many others, that these patients should be hospitalized for study at least three or four weeks before the end of gestation. At the time of hospitalization, the diabetes can be studied once more, and if everything is under control, nothing need be done. On the other hand, if there is some indication for termination of pregnancy, such as evidences of a toxemia, an excessively large baby, or if the diabetes is difficult to control, we would consider the termination of the gestation.

We usually do a pelvic examination, and if the cervix is ripe, that is, if the cervix is soft and the canal patulous, admitting one or two fingers, we feel justified in rupturing the membranes and allowing the patient the opportunity to demonstrate if she will go into labor. If she does, she is likely to have a normal and uneventful delivery. If she fails to go into labor and delivery is indicated by existing conditions, a cesarean section can be done. Whether or not pitocin is used is of secondary importance. On the other hand, if it is decided the pregnancy should be terminated and conditions are not favorable for the induction of labor, then certainly cesarean section is the treatment of choice.

MODERATOR DUNCAN: Dr. Taylor, will you comment on the congenital abnormalities seen in children of diabetic mothers?

DR. TAYLOR: That is a very alarming complication because pregnancy that otherwise goes along well may end in disaster because of serious congenital abnormalities. Going back to Dr. Palmer's first question, I think it is very important that ketosis be well under control at the time the patient conceives and even before that. Patients who tend to run a low degree of acidosis are the ones that often have a congenital abnormality in the fetus. This is because of the effect of acidosis in early fetal environment.

In the diabetic, the preconceptional and early conceptional weeks should be given attention as well as the last eight months of pregnancy. It has been my feeling that the high numbers of congenital abnormalities seen are probably a result of poor control of the diabetic patient in the months previous to gestation and the early weeks of gestation.

MODERATOR DUNCAN: I have been told by our roentgenologist that X-ray pictures taken through the pelvis in the early weeks of pregnancy may increase the incidence of congenital disorders. I should like to ask the panel if this is so. Are congenital abnormalities more frequent or may they be caused by X-ray studies in the early weeks of pregnancy in diabetics?

DR. TAYLOR: I should like to answer for my part that there is no reason roentgenograms cannot be taken at any time during the pregnancy. The amount of radiation that the fetus receives is unlikely to do damage.

DR. DAVIS: We recently investigated the literature on this score and found little evidence that the amount of radiation a fetus receives during diagnostic procedures is likely to do harm.

MODERATOR DUNCAN: Thank you, Dr. Davis. Are there any other comments on this from the panel?

Dr. White, what is your present schedule of female hormones used during pregnancy?

DR. WHITE: Our current schedule depends upon our classification of fetal hazard. The subclinical diabetic, the one in whom the diagnosis is made on the basis of a glucose tolerance test, will receive none, unless there is some special indication.

Patients with diabetes beginning in adult life, or with diabetes of less than ten years duration, and with diabetes beginning between the ages of ten and twenty, but with no vascular damage, receive an ascending dose level of a daily intramuscular injection of 25 mg. of stilbestrol and 25 mg. of progesterone at the 20th week, 50 mg. at the 24th week, 100 mg. at the 30th week, and 125 mg. at the 34th week.

The cases of really severe diabetes starting under the age of ten or with the duration of more than twenty years or with vascular damage, start with 100 mg. of each at

the 20th week, 125 mg. at the 24th week, 150 mg. at the 30th week and 200 mg. at the 34th week. The dosage is regulated either clinically or chemically.

MODERATOR DUNCAN: In determining whether pregnancy is permissible or not, Dr. White seems to be concerned chiefly with fetal and maternal mortality. Dr. White, what consideration should be given the effect of the mother's probable blindness when she starts with a severe retinopathy and her ability to rear the child?

DR. WHITE: I think that is a very important social question, but I haven't thought it was my right to make that decision.

MODERATOR DUNCAN: Dr. Palmer, does pregnancy permanently increase the severity of diabetes?

DR. PALMER: I don't know that that is a good question to ask me. My total experience with pregnant diabetic women only represents 165 cases. That is probably less than 20 per cent of what Dr. White's experience has been. I think she had better answer that.

DR. WHITE: In spite of the fact that pregnancy is diabetogenic, almost immediately following delivery the patient's insulin requirement will drop, usually to the prepregnancy level.

We wonder if our management of a normal pregnancy in the diabetic may not be something like the Houssay, Foglia, Rodriquez experiment, for twenty-six of our unselected cases have been evaluated by a statistician, and the insulin trend curves have been significantly reduced.

A simple example: An 80-insulin-unit case, five to seven years after pregnancy, is well-controlled with eight, ten or twelve units. This has not happened in all cases, but in a striking number.

Diabetic girls, too, remain in much better physical condition than our young diabetic males.

DR. PALMER: Now I am compelled to say something. I am not at all sure that it is the pregnancy that produces this improvement. Consider a diabetic girl who becomes pregnant and wants a child. She is awfully good for eight or nine months, and gets very good care from Dr. White. I am not at all sure that this care does not produce a milder diabetic.

As for any great increase in the severity of diabetes, I have never seen it.

MODERATOR DUNCAN: While you are on that subject, Dr. Palmer, we know that certain of these patients are profoundly sensitive to insulin for a period of several days following delivery—much the same situation as occurs in some patients with acute myocardial decompensation. Would you comment on the modus operandi of this?

DR. PALMER: All I know is what the endocrinologists tell me about that. It is said to be a readjustment of the change in the pituitary influence that takes place during pregnancy reversing toward normal.

MODERATOR DUNCAN: Dr. Taylor, what are the indications for cesarean section in these patients?

DR. TAYLOR: The indication for cesarean section in diabetes is usually a fetal indication. One error frequently made is to think of cesarean section automatically, just because a patient has diabetes and is pregnant. Each case should be individualized, and cesarean section should be done for obstetrical indications such as a really large baby or a small pelvis.

There is also this magic 21-day formula. We know that the child may die in the uterus during the last month of pregnancy, and many of us have accepted it as desirable to effect delivery 21 days early. If induction of vaginal delivery is not feasible for obstetrical reasons, a cesarean section may be done three weeks before term.

The indication for cesarean section is a fetal indication. We should deliver the child by the best method for the individual patient approximately three weeks before term —that may be cesarean section, and it may be vaginal delivery. It depends on how the obstetrician sizes up the case and how he thinks he can most expeditiously deliver that patient of a living normal fetus.

MODERATOR DUNCAN: Would you suppose that delivery three weeks early is advisable because the child is too mature to remain in the uterus to the full term? It might reach maturity three weeks early, but if the trigger mechanism that starts labor is delayed and if the cesarean section is not performed, intrauterine death could result.

DR. TAYLOR: You have summarized the theoretical aspects of this question, and there is little more to say about it except that all the answers are theoretical. The clinical point is that many pregnant diabetic patients have had the experience of having a silent intrauterine death, and for that reason, many of us feel that we should follow the program of delivering the child at least three weeks ahead of term.

It is hard to reconcile postmaturity with the contrary point of view when the baby is in the nursery. Five minutes after delivery, we are told, "Treat it like a premature," so how can you talk about postmaturity before delivery and treat it like a premature delivery? I don't know what the answer is.

MODERATOR DUNCAN: I hope that if they have any ideas, any of the other members of the panel will just break in.

DR. WHITE: Do you think the placenta is too mature rather than the baby? I think the baby is premature by behavior. It may be the placenta matures too rapidly.

DR. TAYLOR: That is a good theory. I don't think there is histological or chemical evidence for that, that I know of.

MODERATOR DUNCAN: Dr. Davis, what are the effects of the estrogenic hormones on the incidence of pregnancy complications in nondiabetics?

DR. DAVIS: I think somebody loaded that question. It depends entirely on whether you are in Boston or whether you are in Chicago. If you are in Boston, it is supposed to decrease the hazard of the late complications of pregnancy. It is supposed to decrease the incidence of toxemia of pregnancy and when toxemia occurs, it ameliorates the course of the toxemia.

Theoretically there is a decrease in the incidence of premature babies born following administration of stilbestrol prophylactically. These premature babies are supposedly larger and stronger and perhaps even smarter.

We recently completed a controlled clinical study in which 1000 patients were administered stilbestrol beginning with 5 mg. and increasing the amount at biweekly intervals to 150 mg. at the 35th week of gestation. Simultaneously we administered placebos to an equal number of patients. To make a long story short, there were no differences in the end results in regard to the baby or the mother as far as the incidence of the various complications of pregnancy are concerned.

Now, mind you, this experiment concerns the prophylactic administration of diethylstilbestrol. It had nothing to do with the administration of this estrogenic hormone therapeutically.

MODERATOR DUNCAN: The alarm reaction is well under way. I would like to ask Dr. Palmer this question. How sound is the physiological basis for the use of estrogenic hormone in diabetic pregnancies?

DR. PALMER: You flatter me. I am not a physiologist. Dr. White is a more expert physiologist than I am. Dr. White has always criticized me because I always give diethylstilbestrol orally rather than parenterally and only on one group of our four groups of cases have I used progesterone.

I could not say that our experience leads us to believe that if you took Dr. White's hormone program home with you and you didn't take a lot of other things that she does with pregnant diabetic women home with you, that you would be much more successful than you are without them because the whole teamwork, the whole setup of the program, is the important thing. You understand Dr. White and I are friends, you know. I would say that if you had to take everything away except one thing, then I would say allow exact control of the diabetes to remain.

DR. WHITE: In many ways I agree with Dr. Palmer. I can only report my own experience, that I can't duplicate my own results without female sex hormones. People think I have no controls, but actually, since 1936 we have had 151 carefully studied and treated cases who received no female sex hormonal therapy, but otherwise have been treated in exactly the same fashion as our other patients, and the fetal mortality in that group of viable cases after is 31 per cent, whereas, our fetal mortality in 594 patients who have received therapy is 11.6 per cent.

MODERATOR DUNCAN: Dr. Davis, do large doses of diethylstilbestrol and progesterone increase the incidence of edema formation?

DR. DAVIS: I can't answer that question. My impression is that it does not increase the incidence of edema. I think that it doesn't influence the edema.

DR. PALMER: Either the mother or the baby?

DR. DAVIS: Neither mother nor baby.

MODERATOR DUNCAN: What would you say accounts for the edema of the baby we hear so much about? They have more of that, I think, in Boston than in Philadelphia.

DR. DAVIS: The babies have a lot of edema in Chicago, too. I think that the edema, the increased accumulation of fluid in the amniotic cavity, perhaps even the pulmonary complications which follow delivery of these very large babies, all are due largely to the edema.

The patient who has little or no edema, as you can determine it on clinical observation, is likely to fare very well. The patient who develops edema is likely to have an excessive accumulation of fluid in the amniotic cavity, and will probably give birth to a baby excessively edematous who will fare poorly following delivery.

MODERATOR DUNCAN: I have three questions in one from one of the panel for the audience.

First, we would like a show of hands of those who use progesterone and stilbestrol as routine in the management of these patients. (Five.)

Second, those who use stilbestrol alone. (Eight.) Increased number.

Those who use no hormones at all. (Many.) Thank you very much.

DR. PALMER: Dr. Duncan, if we are going to leave that hormone question, I would like to say this. My great feeling of deficiency in dealing with the hormone

problem is when to use them, and when not to use them, and the lack of indications to tell me whether or not to use them. There is some doubt in my mind as to the advisability of using them, when they are not needed. In other words, when there is no deficiency and need for them, when I administer them, can I do harm? I would like to pose that question for the panel.

MODERATOR DUNCAN: Is there any comment?

DR. WHITE: I am sure we have treated patients who didn't need it, but we feel convinced we have not done either temporary or permanent harm.

MODERATOR DUNCAN: Another question directed to Dr. White: Do you administer hormones to all cases of pregnancy complicating diabetes?

DR. WHITE: All that come early enough. A few of them come just for delivery, and they escape. (Laughter.) We do not treat our patients who are in the subclinical group. Patients who do not require insulin do not receive female sex hormones.

MODERATOR DUNCAN: I think I shall direct this question to Dr. Palmer. What special precautionary tests and management should be given the pregnant woman when diabetes becomes evident for the first time during pregnancy?

DR. PALMER: I assume that diabetes now develops during the pregnancy, having been previously unknown. Certainly everything you would do for any diabetic should be done. The one thing I would caution against is overlooking the onset of diabetes during pregnancy and treating it lightly as a glycosuria of pregnancy. It is a common time for true diabetes to become manifest.

Obstetricians certainly should always go into the diabetic family history, and should be much more watchful for the onset of diabetes where there is a positive family history of diabetes and also the history of delivery of large babies in previous pregnancies. We have all seen the results of ignoring glycosuria.

The pregnancy may only bring the condition temporarily to the fore as a frank diabetes, and as pregnancy passes the diabetes may recede, later to return even more severely, possibly not until the next pregnancy. If you overlook mild diabetes during pregnancy, some day you will regret it.

MODERATOR DUNCAN: Next is an open question to the panel. It concerns a case report. A woman, aged 33 years, has had diabetes for fifteen years. The third of five pregnancies reached term with delivery of a viable infant by cesarean section. Now three months pregnant, she has early retinopathy, and x-ray evidence of sclerosis. Would you continue with pregnancy or terminate it? Should the question of sterilization be considered? Dr. White, will you start?

DR. WHITE: If there was normal plasma nonprotein nitrogen, I should not think there was a medical reason for induction of abortion in this case. We have had so much difficulty with psychological problems after sterilization, that we avoid it whenever possible. I should permit this patient to continue her pregnancy.

MODERATOR DUNCAN: Dr. Davis.

DR. DAVIS: I should consider carrying this pregnancy, if the patient wants another baby. However, if she has evidences of damage such as have been described, I should consider the termination of the pregnancy. As far as sterilization is concerned, if a patient who has had diabetes for seventeen or eighteen years and has had three children, doesn't want any more children, I should certainly consider terminating her childbearing career.

DR. PALMER: Doctor, would you sterilize the woman or her husband?

DR. DAVIS: We are essentially midwives. We sterilize the woman. (Laughter.)

MODERATOR DUNCAN: Dr. Taylor, have you any comment? Doubtless, the physician who submitted the question wants to know what to do when he goes home. So far we have two votes in favor of carrying the pregnancy unless there are extenuating circumstances. What would you do?

DR. TAYLOR: I think it would be open for discussion on a socio-economic basis more than on a medical basis.

MODERATOR DUNCAN: Dr. Taylor, would you comment on acidosis and fetal death?

DR. TAYLOR: My experience has been largely accumulated in the city and university hospitals and many of the fetal deaths are in cases in which diabetic acidosis develops. I have noticed that some good internists with whom I have worked will pay a great deal of attention to calories, insulin and blood sugar tests, but do not educate the patient to test for acetone in the urine at home. I think such tests are important.

I have seen patients have acetone in the urine, especially in the summer time, when they come to my office and when I ask if tests have been made previously, I find that none have been made by either physician or patient.

I think it is important for internists to test the urine for acetone and to teach patients to make tests, but the obstetrician should not be the one to call it to their attention. (Laughter.)

DR. PALMER: That is a great reflection upon the diabetologist. (Laughter.)

MODERATOR DUNCAN: Dr. Palmer and Dr. White,

have you any comments on acidosis and fetal death?

DR. WHITE: I think that in the second trimester the fetus is particularly susceptible. I am glad to comment that I have written loosely on this subject. In trying to emphasize the occurrence of fetal mortality even without acidosis, I may have given the impression that acidosis is not important. It *is* very important.

DR. PALMER: Acidosis is something to be concerned about under any circumstances whether the patient is pregnant or not. But when the patient is pregnant, I am terribly concerned about acidosis and I watch it very closely. I would want to treat it energetically because I do think it will increase the fetal mortality. All well-informed diabetics should be taught how to test for acetone.

MODERATOR DUNCAN: If one finds acetonuria or symptoms suggesting ketosis, I think it is particularly important to take a sample of blood, spin it down and test the plasma for ketones because if ketones have begun to accumulate in the blood to the extent that they are detectable by a crude test, that patient is headed for danger unless she receives very energetic treatment.

Dr. White, have you an explanation for the large size of many of the infants at birth?

DR. WHITE: These infants are tremendously fat as well as edematous. Although the skeletal growth is somewhat greater, I think the large size is primarily due to fat. There are many interesting possibilities. It might be an insulin effect, since at autopsy the infants either show hyperplasia or a high ratio of beta to alpha cells. Another possible factor is cortisone. Dr. Hoet has the interesting concept and description of these infants as Cushing in type.

MODERATOR DUNCAN: Dr. Davis, what is your plan for the care of the diabetic mother during labor?

DR. DAVIS: The important part of the management of the patient during labor is control of her diabetes. I think everything else is of secondary importance. The more carefully her diabetes is controlled, the less likely you are to have any problem. As far as anesthesia is concerned, it makes little difference. Most of our patients are delivered under regional anesthesia. It is better for the baby and perhaps it is better for the mother, too.

MODERATOR DUNCAN: Dr. Palmer, will you outline your plan for prenatal care of the newborn infant?

DR. PALMER: I think that wherever possible you should have the co-operation of the internist, the obstetrician and the pediatrician. If the functions of these three specialists have to be assumed by one individual, he has to carry a triple responsibility. It is a difficult thing to do.

All of our babies have pediatric care from the time the child is delivered. The responsibility is given completely to the pediatrician. We use incubators and treat them as immature children.

One thing Dr. White does, we haven't done—aspiration of the stomach—because of difficulty in doing it safely without experienced help. But we dehydrate them. We don't give them any fluid sometimes for as long as forty-eight hours or longer, especially if they are wet babies. I do think aspiration of the stomach is important, if you have the ability at hand to do it.

We are not concerned about their blood sugar levels. I have never thought we ever lost an infant in the nursery from hypoglycemia. We follow blood sugars for a long time. (Since this panel, we had a blood sugar in a newborn infant of 18 mg. per 100 cc. and the child survived.)

MODERATOR DUNCAN: Dr. Taylor, have you any comment on this danger of hypoglycemia?

DR. TAYLOR: Our pediatric department does not concern itself with that. They put the baby in oxygen in the Trendelenburg position and withhold fluids from the child for twenty-four hours. It is remarkable to see how much weight is lost in that first twenty-four hours.

I would say mostly it is summed up in that kind of intelligent neglect.

MODERATOR DUNCAN: I am very much interested in this question of fluid because our treatment is quite different. In 1932, we lost a baby apparently because of hypoglycemia. The blood sugar was 20 mg. per 100 cc. by the Folin-Wu method, so the true sugar may have been much lower. I assume it was. At autopsy no abnormality was found except marked hypertrophy of the islands of Langerhans. I thought that that baby died of hypoglycemia. Since 1932 we started feeding the babies immediately after birth, and they are fed every two hours, at least for the first three days.

I would like to go along a little further because in the literature the claim is that the danger is respiratory tract difficulties, and in the one baby we lost at another hospital in the past year, the pediatrician hadn't fed the baby at two-hour intervals, and at autopsy the baby showed pulmonary atelectasis. I would like to ask the panel, wouldn't the baby have been more apt to have pulmonary atelectasis if he were hypoglycemic?

DR. TAYLOR: No. The child is atelectatic at birth. The child never breathes, or breathes with only a segment or two of the lungs. They never open up. I don't know how you can associate hypoglycemia and atelectasis.

DR. WHITE: I think we have seen true hypoglycemia two or three times; those infants need treatment. I feel

our patients really have this hyaline membrane disease rather than hypoglycemia although there isn't a connection between the two.

DR. DAVIS: It is my impression that the babies die a respiratory death as a result of hyaline membrane disease.

I think cesarean section contributes to the likelihood of the development of hyaline membrane disease. For that reason, I feel that when patients deliver uneventfully through the birth canal, their babies have a better chance of surviving and not developing this complication.

Theoretically, the hyaline membrane disease is almost limited to the premature who is delivered by cesarean section. The large baby of the diabetic mother is a premature very often and its size is misleading.

MODERATOR DUNCAN: Dr. Taylor, would you comment on amniotomy for hydramnios and other methods of treatment?

DR. TAYLOR: We have been very unfortunate in trying to prevent hydramnios by any of the methods such as ammonium chloride or mercurial diuretics. They don't seem to do anything to the hydramnion in either prevention or cure. Of course, the thing that always worries one when hydramnion starts to demonstrate itself, is the possibility the child has a serious congenital abnormality such as hydrocephalus.

We have in a few occasions done an amniotomy. I think that is a worthwhile procedure if you can show to the best of your ability that the child does not have absence of the head or some other serious condition. That can be repeated several times during the last few months of pregnancy. However, it isn't always rewarded with a successful outcome.

MODERATOR DUNCAN: What is the best method of anesthesia in delivery of those patients during cesarean section?

DR. TAYLOR: Our clinic uses spinal in cesarean section. We use local infiltration of the perineum, supplemented with some light gas like trilene analgesia or cyclopropane anesthesia for vaginal delivery.

MODERATOR DUNCAN: Do you worry about the increase in diabetes in the population by allowing diabetic women to have children?

DR. WHITE: I am afraid I do. We have studied 204 children of diabetic parents in the past three years. It turned out that both parents of 19 of these children were diabetic, the second parent having been identified as a diabetic during the investigation. Of offspring under age of twenty, 62 per cent had either clinical or chemical evidence of diabetes; in 36 per cent, it was clinical. Of 100 children of diabetic mothers, again under the age of 20, the total incidence of diabetes was 23 per cent; in 9 per cent, there was clinical evidence of diabetes. Of 85 children of diabetic fathers, there was clinical and chemical evidence of diabetes in a total of 21 per cent, clinical evidence in 9 per cent.

We have thought possibly the internal environment might be an important factor in the production of diabetes, but with these new figures, this does not seem to be the case.

MODERATOR DUNCAN: Considering the expected pattern of altered adrenal steroid secretion during pregnancy, do you think that any diabetic with even the slightest evidence of vascular disease should become pregnant?

DR. WHITE: I don't think we have seen increased severity of vascular lesions subsequent to pregnancy. Considering eyes, kidneys and arteries, the female young diabetic is in better condition than the young diabetic male.

MODERATOR DUNCAN: Is any member of the panel familiar with the results of an English study of the effects of stilbestrol in diabetic pregnancies?

DR. WHITE: I heard an unofficial report that there was no difference, or that the patients who received stilbestrol perhaps had had an even higher fetal mortality than those who did not. I would like to point out in many ways this was not a carefully controlled experiment. The patients received what I would call homeopathic doses of stilbestrol, 50 mg. being the maximum. There was no classification of patients according to duration, severity and age of onset, and the total number studied was really not large.

MODERATOR DUNCAN: How effective is rupturing the chorionic membrane in inducing labor successfully enough to bring about premature labor at the 36th to 38th week?

DR. DAVIS: It is a very effective procedure, providing suitable conditions are present. In other words, if there is evidence of rather complete cervical effacement and some dilatation, the rupture of membranes will induce labor without any difficulties in perhaps all of the patients, certainly in 95 per cent of them.

MODERATOR DUNCAN: Will you comment on postpartum changes in the insulin requirement, Dr. Palmer?

DR. PALMER: Dr. White has already commented on that to some extent. I would think probably the fairest and quickest answer to that is that most of our pregnant diabetics return to their prepregnancy requirement level.

MODERATOR DUNCAN: What is the effect of lactation on dietary and insulin prescriptions? We find these

patients do not lactate so we never depend upon it. What is the experience of Dr. Taylor?

DR. TAYLOR: That's right. They practically never lactate.

MODERATOR DUNCAN: What evidence is there to justify routine induction of labor prior to full term? That question would be directed to you, Dr. White.

DR. WHITE: The high incidence of intrauterine death after the 35th week, our peak; I think this is true of most series, in the 36th week.

MODERATOR DUNCAN: Now, what are the ideas that the panel members would like to leave with the audience? Dr. Davis, have you any particular message you would like to put across that you haven't been asked about?

DR. DAVIS: The only message I would like to leave with the doctors here is that the most important part of the management of the diabetic patient is management of her diabetes. If you can control her diabetes carefully and keep her in good control, the chances of her having a living baby are excellent. Whether you administer estrogenic or progestional substances, I think, is of secondary importance.

MODERATOR DUNCAN: You wouldn't agree with the free diet plan, then?

DR. DAVIS: No.

MODERATOR DUNCAN: Those who use the free diet plan have two strikes against their patients because their severe diabetics are never well-controlled, and so they have no well-controlled group to compare them with, whereas those of us who believe in good control of diabetes always have a large number of patients who do as they are told; the diabetes is well-controlled. But we also have that group that do as they like and go on a free diet, so we always have these two groups ahead of us; those that go on a free diet and those who do as they are told. I can assure you that nearly 70 per cent of my readmissions to hospitals come from the smaller number of patients who do as they like.

DR. PALMER: May I say just a word? I think that doctors and diabetics have been so sold by our profession that you can take insulin once a day, that they try to carry that plan through pregnancy. I don't know how many patients Dr. White has to put on a multiple insulin injection program, but I feel that we have erred very much in the past by not doing so with sufficient frequency and thus accomplish better control. At the moment, I advise control of diabetes to the best of our ability even if we give insulin three or four times a day.

MODERATOR DUNCAN: I agree most heartily with Dr. Palmer. Dr. White, would you comment on the value of examining for glycosuria during pregnancy and the pitfalls that are in it?

DR. WHITE: I think that glycosuria should be taken very seriously during pregnancy and that any pregnant patient with glycosuria should be evaluated with a glucose tolerance test. In the past, if the glucose tolerance test was positive, we have treated most of these patients with dietary regulation alone, and then if this did not control hyperglycemia, have added insulin. You are probably familiar with Professor Hoet's interesting thought that in order to prevent the subsequent development of diabetes, these patients should be treated with as much as sixty units of rapidly acting insulin a day. We have never given such doses to patients of this type.

MODERATOR DUNCAN: Is it so that approximately 10 per cent of nondiabetic women have glycosuria during pregnancy because of a low renal threshold?

DR. WHITE: Some figures are as high as 60 per cent.

MODERATOR DUNCAN: Yes. Had you any other idea, Dr. White? I asked you a question and didn't give you an opportunity to get a special idea across.

DR. WHITE: I would like to emphasize the yearly evaluation of the child, even the young child of diabetic mother or diabetic father for the possible evidence of subclinical diabetes.

MODERATOR DUNCAN: Thank you. Doctor Palmer.

DR. PALMER: No one has discussed determination of the duration of pregnancy. X-ray examination of the fetus beginning at the 34th week to observe the appearance of the epiphysis in the femur has been exceptionally helpful with us. The femural epiphysis appears by X-ray at the 36th week.

DR. TAYLOR: No one could pass up the opportunity for a last word. What I should like to suggest is that at least in our field of obstetrics there are very few controversial elements left, but diabetes and pregnancy is one. A plan is being worked out by one of the subcouncils on therapy of the American Medical Association to study this controversial subject in a country-wide fashion through several large clinics. Many of you will have opportunity, if you have not already, to participate in this through your obstetrical services. There are three types of treatment in regard to the use of hormones—the Priscilla White plan that she has outlined, using both stilbestrol and progesterone; the Smith and Smith plan using stilbestrol alone, and then the nihilistic school using no hormones. Until this study is completed, we shall still have these interesting and controversial panels concerning the usefulness of hormone preparations in diabetes and pregnancy.

MODERATOR DUNCAN: What is the concensus of the panel on the use of hormones in diabetes pregnancies?

DR. PALMER: You mean the audience doesn't know the answer to that yet?

MODERATOR DUNCAN: I take it you all use them!

DR. DAVIS: We all use them? No.

MODERATOR DUNCAN: No. Dr. Palmer.

DR. PALMER: Dr. White uses them; she has told you when she uses them and all about it. I have used them, but I am still confused in my own mind as to how much of an influence they are. I wish I had a test of some kind to tell me when to use them.

DR. TAYLOR: We do not use them.

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## *Employment For Diabetics*

The American Diabetes Association has emphasized its philosophy that a controlled diabetic is a good employment risk. Also, by virtue of his capability of performing a full day's work satisfactorily despite his disease, the diabetic should not be classed with the physically handicapped. During the past five years, the Association, through its Committee on Employment, has endeavored to reach some unanimity of opinion in the formulation of recommendations to labor and management regarding the industrial utilization of the diabetic. The structure of the Committee is of interest, for extramural members were sought from the United States Civil Service Commission, the United Mine Workers of America, the Industrial Hygiene Foundation, and the Diabetes Section of the Public Health Service. There was additional contact with the Office of Vocational Rehabilitation of the Federal Security Agency and with the Association of Railroad Engineers.

Mildly diabetic persons, in no need of insulin, present no employment problem. Of persons with severe diabetes, with both insulin and regulated-diet needs, there is the well-controlled and well-regulated patient and the unco-operative and poorly regulated patient. The latter, if hired, would prejudice employers against all diabetics, for they not only are poor work risks because of their diabetes but are potential absentees in the light of complications to come. The well-controlled diabetic has proved his worth and his employment stability in hundreds of organizations employing such persons.

Standards suggested by the Committee for both employers and prospective workers with diabetes, in essence, are these: 1. A diabetic seeking employment should present a note from his physician stating that he is controlled and undergoes periodic examinations. 2. Diabetics can perform any work for which they are equipped physically, mentally, and educationally. Those taking insulin in large doses should not be assigned to work wherein hypoglycemic attacks would injure either them or others. 3. Diabetics should work straight shifts (unbroken and nonrotating). If a rotating shift is necessary, they should avoid the midnight to 8 a.m. schedule. This is the only concession in terms of hours that a well-controlled diabetic should ask. 4. Certain key personnel in a plant employing diabetics should be familiar with the nature of diabetes and the possibility of coma or insulin reactions. 5. Diabetics should carry cards or tags identifying their condition. 6. The plant physician, in co-operation with the diabetic employee's family physician, should perform periodic blood and urine examinations, if the patient's work schedule precludes visiting his regular laboratory facilities. 7. Each diabetic should have a complete annual physical examination. 8. Transfer or reassignment of a diabetic at the request of the plant physician, when new complications create new risks, is a justified procedure. 9. An insulin-requiring diabetic is considered controlled if his fasting blood sugar is not below normal limits and not over 150 mg. per 100 cc. (Folin-Wu method), if the level after a meal is not higher than 250 mg. per 100 cc., and if he is under regular medical supervision.

It is to be pointed out that excellent liaison has been established by the Committee at the national level with the Congress of Industrial Organizations, the American Federation of Labor, and the Railroad Brotherhoods. If necessary this co-operation can be extended downward. With these employment standards in realistic usage by employers and personnel directors, the diabetic applicant should be considered just as eligible for work as the nondiabetic candidate. His effective contribution to industry has been demonstrated, and with continuing co-operative efforts among labor, employers, and professional groups toward hiring the diabetic, employment prejudice will continue to abate.

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# A Six-minute Test with Glucagon-free Insulin in the Classification of Diabetes and Prediabetes

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Somogyi[1] pointed out that conventional tests for insulin tolerance are not adequate for determining sensitivity or responsiveness to insulin, since blood glucose below the fasting level rapidly initiates counter-regulatory mechanisms which promptly mask the degree of response to insulin.

The uncertainty of the period of action of the hyperglycemic factor existing in presently available crystalline insulin makes it quite impossible to appraise satisfactorily the primary influence of the administered insulin on blood glucose in respect to the promptness of initiation of action ("latent period" of Himsworth[2]) and in respect to the unhampered degree of fall in blood glucose. It is essential, therefore, that for a good test of responsiveness these latter two factors be registered before any extensive fall in glucose has had an opportunity to excite the body's counter-effort at homeostatic readjustment. Such time would fall well within the first few minutes after injection of insulin.

The valid criticisms of tests now in vogue for sensitivity to insulin can be obviated by careful timing, using an insulin which is free of the hyperglycemic-glycogenolytic factor (HGF or glucagon). The suggested responsiveness test with glucagon-free insulin records blood glucose readings in a time period before marked reactive compensatory phenomena have come into play, namely within the first six minutes after administration of the insulin. Under such conditions, only factors already residing in the individual and actively functioning at the very time of the injection of insulin could prevent the initiation of a fall in blood glucose. These are anti-insulin factors peculiarly inherent in the individual and possibly actually creating the diabetic state in the obese adult.[3]

## PROCEDURE

As controls, each of forty nondiabetic individuals (medical students and nurses) with no family history of diabetes was given three units of glucagon-free insulin by vein after a sixteen-hour fast. Determinations of the glucose content of venous blood were made with stop-clock timing precisely at 2, 4, 6, 12, 24 and 30-minute intervals after the glucagon-free insulin was administered. The Somogyi-Nelson macromethod for true blood glucose was used.

To obviate repeated venipuncture, a 20-gauge needle was inserted into an antecubital vein and a slow infusion of physiologic saline solution was instituted, thereby keeping the needle patent between blood withdrawals. The volume of saline solution infused during the six-minute period was rarely more than 60 cc. A tourniquet was used only at the time of insertion of the needle, the blood withdrawn at this time being discarded, as were the subsequent two or three samples over an eight-minute period before the sample designated as "fasting" was arrived at.

With regard to adrenal activity incidental to the procedure, every effort was made to place the subject at ease. Blood pressure readings were made before the test as well as frequently during it to detect any unusual play of adrenal response. Simultaneous pyruvate determinations were, however, not made. Glucose determinations on the first two or three discarded blood samples suggested that within eight minutes after the venipuncture the blood glucose had established itself at a fixed basic fasting level, whereupon in subsequent cases the insulin for testing was administered after an eight-minute period. A single team of two persons carried through all procedures, including the blood sugar determinations. Spot

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I am indebted to Drs. Franklin B. Peck and William R. Kirtley of Eli Lilly and Company for the supply of glucagon-free insulin used in this study.

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duplicate determinations were made, especially in event of bizarre readings.

## FINDINGS

The dominant trend of change in blood glucose was well indicated within the first six minutes after the insulin administration, the line of depression thereafter often being interrupted by marked counterregulatory responses. The downward glucose trend then became more gradual and straightened out toward a nadir which usually occurred within the last twenty-four-minute period of the testing. Since in both nondiabetic and subsequently in diabetic individuals the nadir of the glucose curve ultimately arrived at could usually be roughly predicted by the behavior of the blood glucose pattern within the first six minutes of the test, and since, in a significant number of persons, varying amounts of insulin seemed to bear no consistent stoicheiometric relationship to the results obtained, the study was ultimately confined to blood glucose patterns made over a six-minute period after a fixed dose of three units of glucagon-free insulin by vein.

The nondiabetic control subjects usually showed a drop of 19 per cent ± 7 per cent from the fasting blood glucose level within the six-minute period.* Exceptions to this occurred in two types of cases: (1) in the obese but otherwise "normal" adult with normal blood glucose readings and glucose tolerance tests, who frequently exhibited poor responsiveness to glucagon-free insulin within the first six minutes of the test, as in the curves of diabetics presented in figure 2; and (2) in the normal individual whose fasting blood glucose happened to be exceptionally low, in which event further depression usually did not occur (probably a homeostatic defense against excessively low blood glucose).

The six-minute test was subsequently carried out in one hundred cases of diabetes unselected save for reliability of the diabetic history. In many of these the test was performed serially before and after effective treatment. In diabetic subjects customarily receiving insulin, a quick preliminary blood glucose level with the Wilkerson-Heftmann[4] technic was recorded before the test dose of insulin was administered in order rapidly to preclude the existence of any marked initial hypoglycemia before the test was started.

The responses in diabetic subjects conformed with three major distinctive patterns within six minutes after the insulin administration:

(1) The juvenile type of diabetic (at any age) unless markedly out of control usually showed a rapid precipitous drop in blood glucose (figure 1). This decline was with rare exception well on its way to consummation within four to six minutes. The attainment of excessive body weight in the juvenile type of diabetic or even the process of rapid gain in weight was often associated with the development of poor responsiveness to insulin, as in some nondiabetic obese individuals (figure 2). This lack of responsiveness was frequently reversible by weight reduction.

(2) The untreated obese-adult type of diabetic without "brittleness" commonly showed sluggishness of response apparent only after a latent period, a lack of fall in blood glucose, or even a rise to above the fasting level within six minutes after the insulin administration (figure 2). With adequate clinical treatment of the diabetes, including weight reduction, these poorly responsive persons (figure 2), usually showed curves tending to approach the responsiveness shown in figure 1 or anticipated in nondiabetic, nonobese subjects. When the uncontrolled obese diabetic ultimately develops an absolute beta-cell deficiency, his sensitivity (responsiveness) becomes extreme—far beyond the normal (cell paucity proved by postmortem examination).

(3) In the labile or so-called "brittle" diabetic, not only of the juvenile but also of the obese-adult type, there was an extremely precipitous and deep decline within the first two to four minutes of the test, followed by an equally sharp ascent, often to well above the initial fasting level—all within six minutes after the insulin administration (figure 3).

## CONCLUSIONS

1. A practical, speedy clinical test for responsiveness to insulin is presented.

2. Glucagon-free insulin is utilized to avoid extraneous factors which in preparations of crystalline insulin ordinarily available in the United States and Canada counteract and mask the initial and earliest action of injected insulin.

3. Blood glucose values obtained within a six-minute period by this method yielded distinctive curves which permitted classification into three types: (a) the obese-

* Jørgen Pedersen of Copenhagen has pointed to the fact that even in the fasting state blood glucose fluctuates considerably. The average reading of three tests over the six minutes immediately before the insulin can be compared with the low points after injection of insulin. The sizable drop in responsive individuals (19%±7%) precludes the practical need for this.

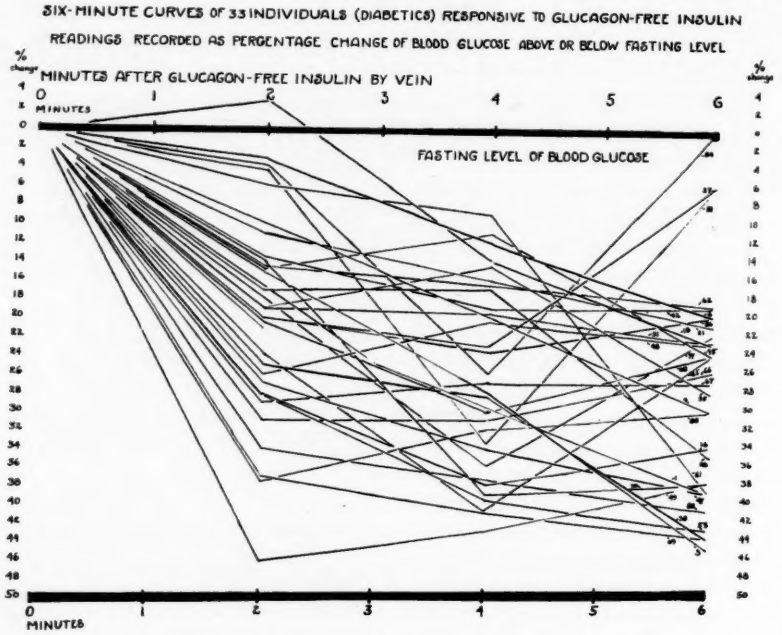
SIX-MINUTE CURVES OF 33 INDIVIDUALS (DIABETICS) RESPONSIVE TO GLUCAGON-FREE INSULIN
READINGS RECORDED AS PERCENTAGE CHANGE OF BLOOD GLUCOSE ABOVE OR BELOW FASTING LEVEL
MINUTES AFTER GLUCAGON-FREE INSULIN BY VEIN
% change
MINUTES
FASTING LEVEL OF BLOOD GLUCOSE
0 1 2 3 4 5 6

FIGURE 1

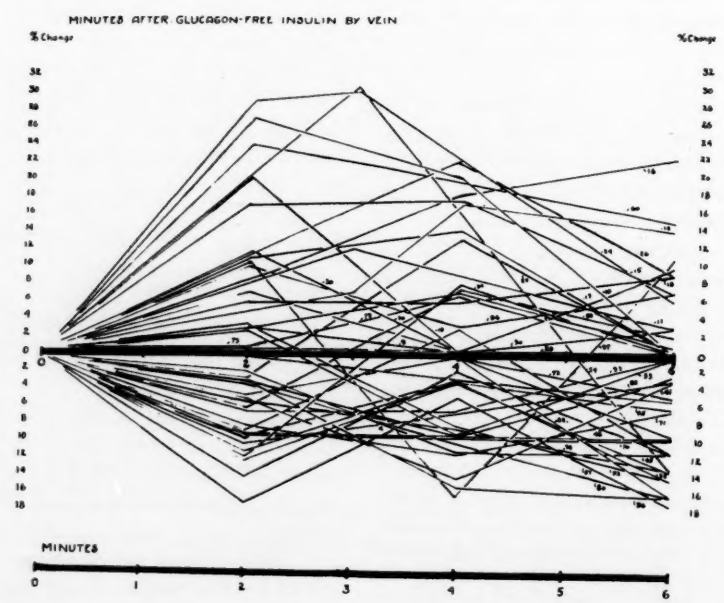
SIX-MINUTE GLUCOSE CURVES OF 40 INDIVIDUALS (DIABETICS)
POORLY RESPONSIVE TO GLUCAGON-FREE INSULIN
READINGS RECORDED AS PERCENTAGE CHANGE OF BLOOD GLUCOSE ABOVE OR BELOW FASTING LEVEL
MINUTES AFTER GLUCAGON-FREE INSULIN BY VEIN
% Change
MINUTES
0 1 2 3 4 5 6

FIGURE 2

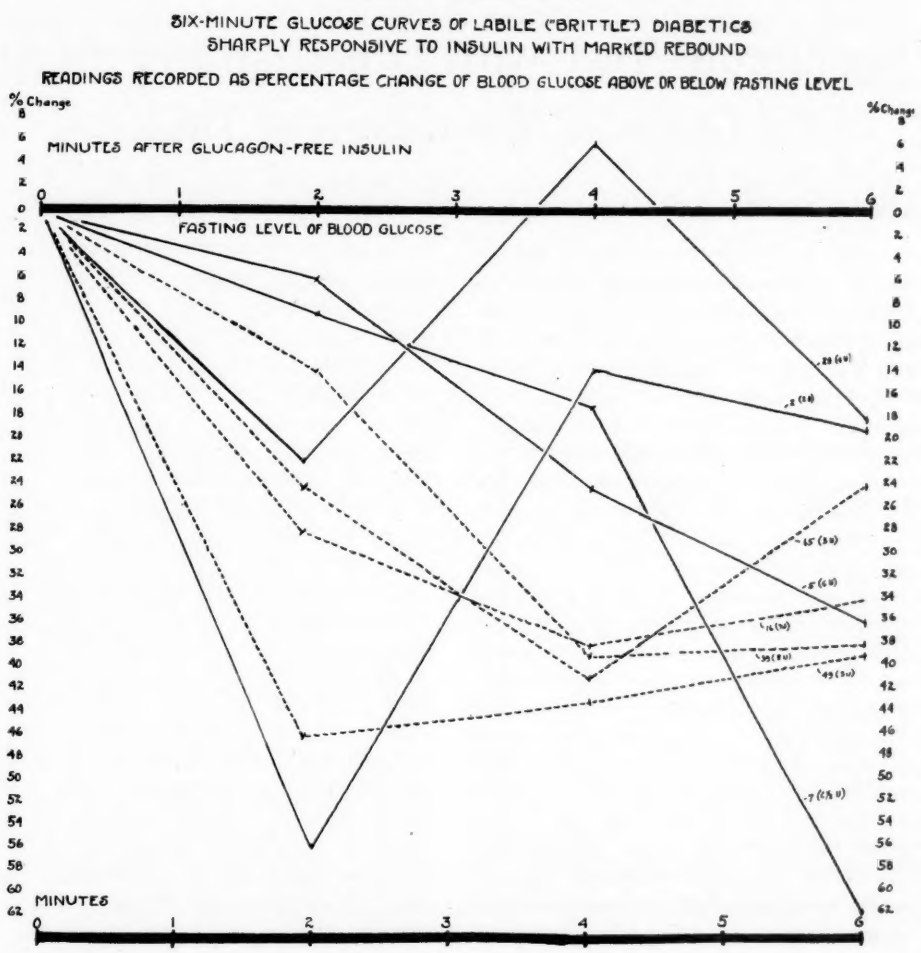
SIX-MINUTE GLUCOSE CURVES OF LABILE ("BRITTLE") DIABETICS
SHARPLY RESPONSIVE TO INSULIN WITH MARKED REBOUND
READINGS RECORDED AS PERCENTAGE CHANGE OF BLOOD GLUCOSE ABOVE OR BELOW FASTING LEVEL
% Change
MINUTES AFTER GLUCAGON-FREE INSULIN
FASTING LEVEL OF BLOOD GLUCOSE
MINUTES

FIGURE 3

adult type of diabetic, before adequate treatment; (b) the juvenile type of diabetic, at any age, unless markedly out of glucose control, when the curve may approach that of (a); and (c) the labile or "brittle" type of diabetic.

4. The impaired responsiveness to insulin in the non-diabetic obese but otherwise "normal" individual, who has normal blood glucose values and glucose tolerance test, raises the question whether faulty responsiveness to insulin as indicated by the six-minute test may not be a more delicate index of potential future clinical diabetes than are these conventional tests now in use.

5. Whatever may be the mechanism involved in the production of the phenomena presented, for example, varying liver glycogenation, labile glycogenolysis, or other explanation, the information obtainable by this procedure is sufficiently definitive and reproducible to serve as one means of classifying diabetics.

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# A Six-minute Test with Glucagon-free Insulin As a Guide to Treatment of Diabetes

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In the treatment of diabetes, the ability of the organism to respond to insulin has not been accorded the attention it merits. This is especially true since it has been demonstrated that in normal individuals responsiveness to insulin is largely contingent on dietary habits.[1-3] Therapeutic efforts have been centered about attaining a reasonably "normal" blood glucose level, whatever may be the method of arriving at this quasi-ideal state. Spot blood glucose readings have been the basis for determining such "normalcy." Certainly, in the diabetic these isolated readings do not necessarily reflect a true picture of the status of insulin function. They can at best present only snapshots of blood glucose status at given instants rather than a dynamic picture of what is actually happening to a function which is probably never static. They portray the end result of an action rather than the mechanism of the action producing it. For example, a patient receiving insulin who shows a blood glucose value of 130 or more mg. per 100 cc. may be in far better glucose economy than is one with a value of only 80 mg. The latter's supernormal level may well represent an artifact of normal suggesting improved insulin efficiency in the individual, a picture which, however, is not at all dependent on improved intrinsic insulin function but rather on a forced and unphysiologic lowering of blood sugar resulting from massive dosage of extrinsic insulin. The ideal reading may well represent a mass stoicheiometric effect of insulin from without rather than the more normal functional role of the hormone, which should act as a delicate and sensitive catalyst even in small dosage.

It is possible to determine within a few minutes of the patient's time by means of a responsiveness test to insulin whether a low glucose reading reflects actual intrinsic improvement or whether it is only an artificial facsimile of such improvement, based solely on large dosage of extrinsic insulin. An individual who is unable to respond normally to insulin usually exhibits a defective six-minute responsiveness test. This fact has sprung from a study of 450 responsiveness curves, many successively and serially followed, under varying circumstances of insulin dosage, dietary regulation, weight status, infection, stress, and degree of diabetic control. If the organism is unable to respond normally to insulin, either from without or from within, the functional effectiveness of that hormone must be adjudged to be impaired at least to this extent. In the individual whose insulin function is not impaired, a small dose should be physiologically effective. With normal ability to respond to insulin there is usually no need for mass effect of the hormone, which constitutes in many diabetics only an artificial intrusion into the picture from without. The error in diabetes usually resides less in the inability of the organism to produce insulin (dosage) than it does in some error in the substrate of the body in which insulin is to act. This fact is well supported by changing findings in the Six-minute Test, which reflect variations in the ability of the organism to respond to insulin as a result of changes in the ground soil induced by diet, infection, anxiety, the adrenal steroids, and excessive extrinsic insulin itself.* These reflections are, moreover, frequently reversible at will by correction of the underlying error.

In judging a patient's insulin efficiency, the promptness of initiation of its action on blood glucose has taken a secondary place to the extent of the ultimate fall as well as to the duration of its recognizable effect on blood sugar. A sluggish initiation of action must be adjudged

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*A patient with insulinoma showed unresponsiveness in the Six-minute Test. This changed after resection of the tumor.

to be a mark of inefficiency even though the ultimate nadir of blood glucose reached after two or more hours may be comparable with that usually to be anticipated in the nondiabetic individual. Presumably, there are active in the diabetic counter-insulin factors which prevent a prompt fall in blood glucose.

Himsworth of London[1-4] pointed out the fact that the "latent" period of insulin effect is definitely influenced by the degree of sensitivity (responsiveness) of the individual to insulin. He emphasized that ingested carbohydrate is normally not only the stimulus to the blood glucose lowering effect of insulin but also the sensitizing factor that makes the individual normally responsive to insulin. Ingested carbohydrate is the trigger mechanism to insulin function.

Just as the nondiabetic person can by adequate ingestion of carbohydrate be made more responsive to insulin administered by vein, so through the agency of adequate dietary treatment, with or without extrinsic insulin, can the diabetic usually be reverted in the direction of normal ability to respond to insulin. Such reversion is not merely of academic significance but represents the reestablishment of the patient's own functioning intrinsic insulin mechanism within the orbit of the other native endocrine systems. An impaired but nevertheless functioning intrinsic mechanism may in many ways be superior to a fixed inflexible artificial modality from without. Lame as the native insulin mechanism may have become, it usually to some extent still functions in homeostatic relationship with the other hormonal mechanisms of the body. Such interrelationship can frequently be improved in the direction of normal by adequate dietary treatment carefully engineered. An intrinsic mechanism which has regained some of its original automaticity is bound to have a more favorable steadying effect on the over-all hormonal equilibrium* of the body than could possibly be achieved by an artificial fixed modality which has been arbitrarily and inexactly inserted into the chain from without. When a large dose of an inflexible agent like extrinsic insulin is interposed in the moving system of endocrine mechanisms, homeostasis is bound to be challenged thereby. All other components of the system are obliged to mobilize and sharply readjust if they are to meet adequately the inexorably fixed action of the intruder.

* Native insulin function may aptly be compared with the modern automobile, the mechanisms of which are carefully timed and spring-cushioned. An oversized or undersized tire (dose of insulin) can upset the delicately adjusted synchronism and result in an inefficient machine's delivering a rough ride.

One can have no possible quarrel with the correct use of extrinsic insulin to meet an absolute deficiency in the organism. The abuse of this modality occurs when it is substituted for a beta cell pancreatic function that by proper dietary measures could have been restored to its native role in the body economy. Treatment with extrinsic insulin, accordingly, serves its best function when its careful administration is aimed at rehabilitating the patient's own insulinogenic mechanism.

The above principle resolves itself into whether it is not worth-while in the treatment of the diabetic to safeguard in physiologic manner the native insulin mechanism from unnecessary further impairment, or even from possible destruction occasioned by attrition or suppression (figure 1).

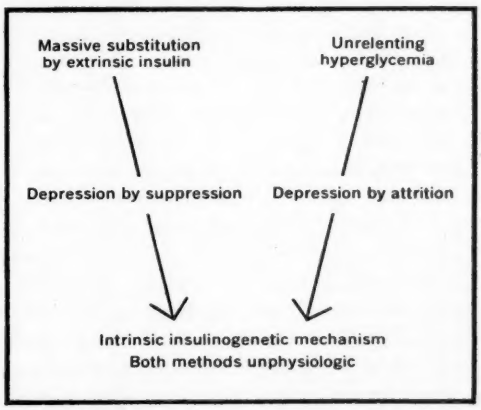


FIG. 1. Reproduced by courtesy of "Postgraduate Medicine."

It has been amply shown that substitution from without for an impaired hormonal function is destined[5-12] to smother what may be left of that function. This is the well acknowledged principle of endocrine *suppression* by excess of the homologous hormone from without. It is the counterpart of impairment of function by *attrition* of the intrinsic insulin mechanism: the steady imposition of unwarranted load, for example, excessive calories or external stress, obesity or excessive pituitary and adrenal steroid factors from within. If one can by treatment counteract one or more of these influences in a manner which results in measurable improvement in the ability of the diabetic to respond to insulin, this accomplishment becomes prima facie evidence that the rationale of treatment is correct.

## THE SIX-MINUTE TEST—FINDINGS

The Six-minute Test effectively indicates (1) whether native insulin function is being suppressed by excessive

extraneous insulin, (2) whether inadequacy of therapy is leading to destruction of the intrinsic function by attrition, or (3) whether the treatment of the diabetes is leading to functional rehabilitation of the impaired mechanism. This mode of appraisal of intrinsic insulin function is based not on a static picture of spot blood sugars, but rather on a measurable and reproducible moving picture of the body's changing ability to respond to insulin.

The Six-minute Test for responsiveness to insulin has been described in detail elsewhere.[13-16] In brief, it is a measure of the promptness and sharpness of the body's response to insulin administered by vein. For this purpose, a single dose of three units of glucagon-free* insulin is given by vein in the fasting state. Venous blood glucose† levels are determined in the fasting state and at two, four, and six minutes after administration of the insulin. One characteristic type of curve indicating defective responsiveness to insulin occurs in obese[13] diabetics: (1) *before* effective treatment to control the glycemia and reduce body-weight, (2) *after* treatment which was obviously inadequate to accomplish these aims, and (3) after treatment which had seemed to be adequate but which, nevertheless, by this test proved to be ineffective. With effective therapy this type of curve is usually reversible to one showing improved or even normal‡ responsiveness to insulin.[13] The unmistakable contrast between the two types of curve speaks for itself. The improved curve is, in turn, frequently reversible to one showing poor responsiveness after a prolonged break in glucose control or in the presence of infection, anxiety, or any other of the known factors which characteristically impair the clinical well-being of the diabetic. Sample before-and-after serial successive curves in relation to treatment are presented in figures 2-9.

Responsiveness tests were performed at random on one hundred patients with the obese-adult type of diabetes and on forty-six patients with the juvenile type. Table 1 presents the collective findings in these patients. Subsequently, forty-six of these patients were serially and successively tested at two- to four-week intervals. The findings are summarized in table 2. Seventy-seven per cent of patients of the adult type, originally poorly responsive or unresponsive to insulin, became responsive under treatment; 66 per cent of patients of the juvenile type who had been unresponsive again became responsive to insulin after adequate treatment.

Eighteen of the one hundred adult-type patients tested showed poor responsiveness after treatment. In all of these, treatment had in all probability really been inadequate, since at the time of the final tests these patients were still from 6 to 48 per cent overweight (excessive weight is inimical to the diabetic). We have no adequate explanation for the failure of therapy in the remaining seven patients who seem to have been adequately treated, they having achieved normal or subnormal body weights through treatment.

## DISCUSSION: APPLICATION OF THE SIX-MINUTE TEST TO THERAPY

The obese adult type of diabetic is thought to suffer not so much from an inability to elaborate insulin as from a chronic excessive demand for insulin which his body cannot meet. His is a relative deficiency of insulin. Uncorrected, such deficit spending of the insulin which he still can elaborate ultimately leads to bankruptcy of his own intrinsic insulinogenic mechanism—impairment by *attrition.*

The juvenile type of diabetic (the thin, wiry individual), on the other hand, suffers largely from an inability to *make* insulin as he normally should, presumably from a lack of functioning beta-cell tissue. His deficiency is, accordingly, in the main absolute or, if untreated, rather rapidly arrives at this absolute state of deficiency. To this absolute insufficiency may, of course, be added a relative deficiency created by an excessive acquisition of body weight, infection, anxiety, chronic stress, hyperthyroidism, hypermetabolism, or other demand load. Clinical diabetes usually represents a combination of relative and absolute deficiencies, with one or the other in predominance.

*"Glucagon" is a term applied by Murlin[17] in 1923 to the hyperglycemic-glycogenolytic factor present in commercially available insulins in this hemisphere. As pointed out by Somogyi,[18] this is one of the factors making it quite impossible adequately to assay by conventional insulin sensitivity tests the promptness and sharpness of the body's responsiveness to insulin. Blood glucose levels below the fasting rapidly call forth counter-regulatory mechanisms which promptly mask the degree of fall in glucose resulting from the insulin injection. Conventional tests, accordingly, better indicate the individual's responsiveness to hypoglycemia rather than to insulin. It is, therefore, essential that readings of the direct and immediate effect of insulin on blood glucose be made before the lowering has had an opportunity to arouse the counter-regulatory reaction incidental to the hypoglycemia—hence, the timing in the Six-minute Test. Blood glucose readings at two-minute intervals after the administration of the insulin make possible accurate appraisal of the "latent" period of Himsworth.[1, 2]

†Somogyi-Nelson macro-method employed.

‡ The nondiabetic, nonobese, "normal" individual usually shows a fall of 19 per cent ± 7 per cent from the fasting level unless this level happens to be extremely low, in which event there is usually no further drop in blood glucose.

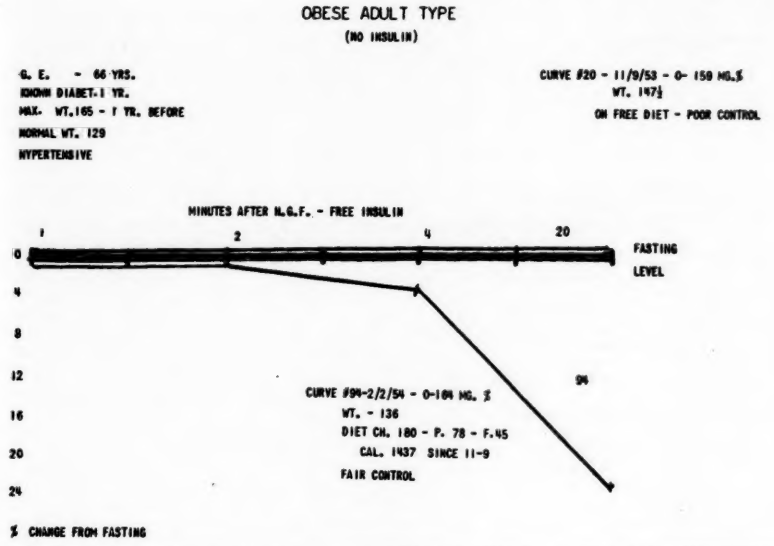


FIG. 2. "Before and after" treatment.

"First curve" (No. 20). Patient after one year of free diet with poor sugar control. Note: No drop in blood glucose during the entire six-minute period.

"Second curve" (No. 94). Approximately three months later, on a measured diet without insulin. Note: Drop in blood glucose after the second minute.

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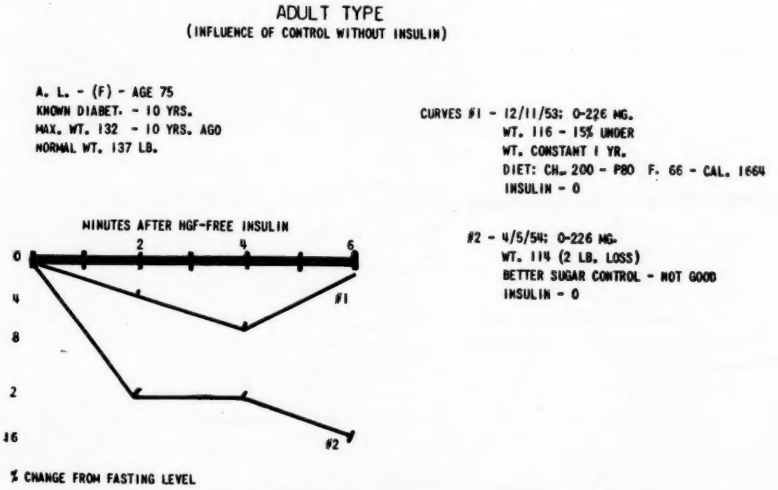


FIG. 3. Influence of dietary control "without insulin" shown. Even though the glucose control is still not perfect at the time of the second curve, four months after the first, with slow loss of weight and better glucose control, there is a decided improvement in the curve. Reproduced by courtesy of "New York State Journal of Medicine."

Before treatment or at a time when glucose control is poor, it is usual to find that the obese-adult type of diabetic is not at all or only poorly responsive to insulin in the six-minute period of the test. Correction of the obesity greatly reduces the load demand for insulin and leads to improvement in the diabetes. The patient who had been poorly responsive to insulin usually makes an about face and regains, at least in part, ability to respond promptly to insulin. The test would, accordingly, appear to support the clinical observation that an excessive caloric burden, whether this be in the form of ingested carbohydrate or fat, or in the form of depot fat, is in the diabetic inimical to native insulin function.

When mild caloric restriction resulting in weight loss and glucose control is not attended by an improvement in ability to respond to insulin (of course, in the absence of infection or other interfering complication), it is wise to revise one's dietary prescription as to its content of carbohydrate. Ingested carbohydrate is the normal trigger mechanism to insulin function.[19] Ingested carbohydrate can, however, act as a stimulus to such function only if the organism is not already in a refractory state resulting

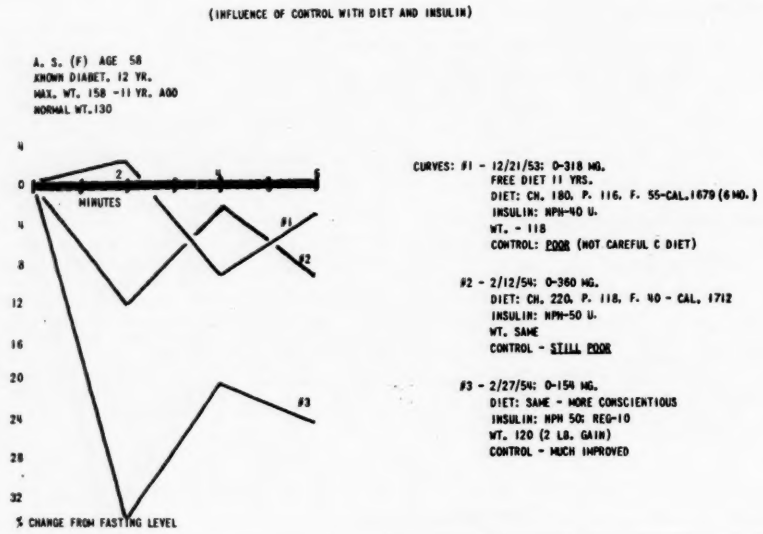
ADULT TYPE
(INFLUENCE OF CONTROL WITH DIET AND INSULIN)
A. S. (F) AGE 58
KNOWN DIABET. 12 YR.
MAX. WT. 158 -11 YR. AGO
NORMAL WT. 130
MINUTES
#1
#2
#3
% CHANGE FROM FASTING LEVEL
CURVES: #1 - 12/21/53: 0-318 MG.
FREE DIET 11 YRS.
DIET: CH. 180. P. 116. F. 55-CAL. 1679 (6 MO.)
INSULIN: NPH-40 U.
WT. - 118
CONTROL: POOR (NOT CAREFUL C DIET)
#2 - 2/12/54: 0-360 MG.
DIET: CH. 220. P. 118. F. 40 - CAL. 1712
INSULIN: NPH-50 U.
WT. SAME
CONTROL - STILL POOR
#3 - 2/27/54: 0-154 MG.
DIET: SAME - MORE CONSCIENTIOUS
INSULIN: NPH 50: REG-10
WT. 120 (2 LB. GAIN)
CONTROL - MUCH IMPROVED

FIG. 4. Curve No. 1. After 11 years of free diet, and six months of a measured diet not conscientiously followed; poor glucose control. Curve No. 2. Five weeks later, after an increase of 40 gm. of carbohydrate. Curve No. 3. Diet prescribed same as at time of Curve No. 2, but more conscientiously followed; "control much improved!" Reproduced by courtesy of "New York State Journal of Medicine."

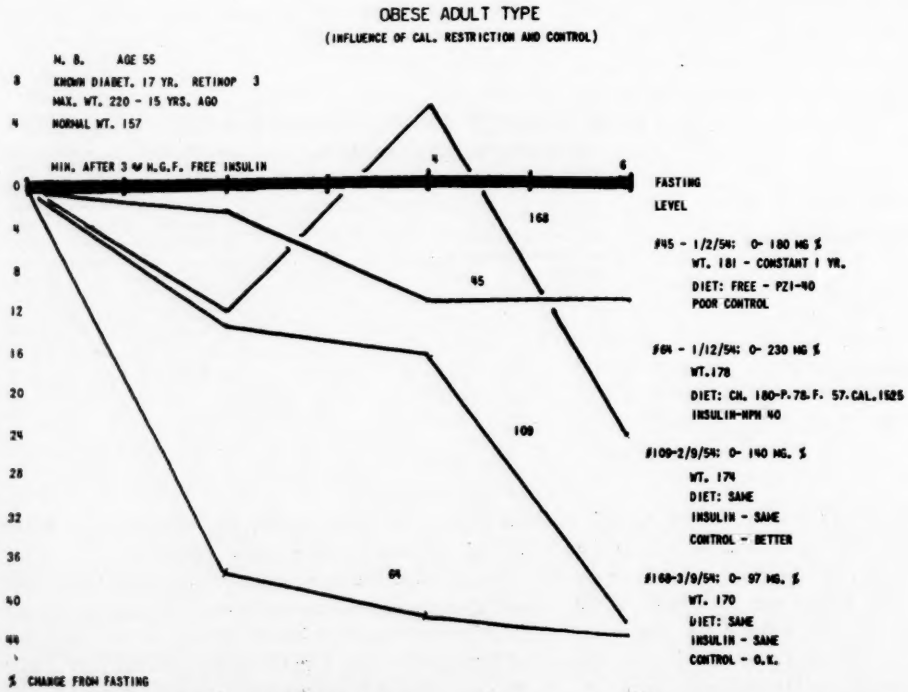


FIG. 5. "First Curve" (No. 45) Taken after 17 years of "free" diet and PZI; had developed grade 3 retinopathy—poorly responsive. "Second Curve" (No. 64) 10 days later (on measured diet)—over-responsive. "Third Curve" (No. 109) about one month later—diet and insulin same as at second curve (No. 64) but better glucose control had been established. "Fourth Curve" (No. 168) 1 month later—control good—responsiveness normal.
Observation: Progressive blindness is a stimulus to conscientious dietary effort on part of patient.

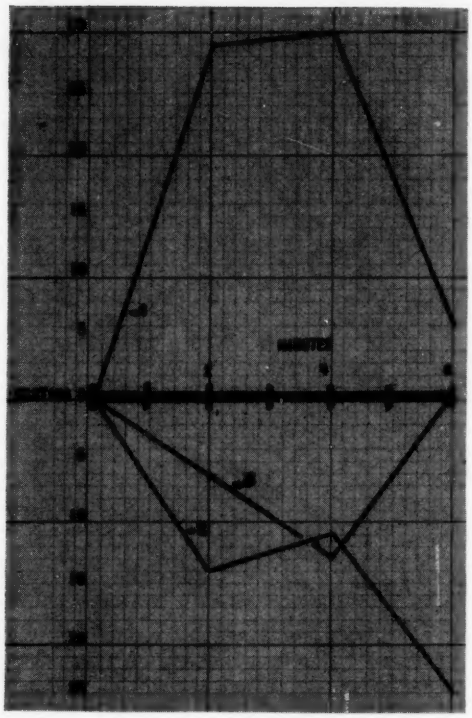

FIG. 6. Influence of carbohydrate in obese-adult type: A patient aged 75 years was known to have had diabetes for 10 years. His maximum weight had been 200 lbs. 10 years before test, (normal weight 141 lbs.). At the time of the first test, curve No. 1, the patient had been on insulin treatment for 10 years; he had used 8 units of NPH insulin and 6 units of regular insulin and a diet C. 180, P. 116, F. 55, for 6 mos. His weight was 131 lbs. Curve No. 1 shows a lack of responsiveness to insulin. (The fasting level in this curve was taken 8 minutes after adrenal activity had spent itself). The second curve (No. 2), was taken five weeks later. The body weight and insulin were the same, but the carbohydrate of the diet had been raised by 40 gm. of glucose. Control was good at all times. This curve represents stimulation of the intrinsic mechanism by ingested carbohydrate. The third curve (No. 3) taken eight weeks later shows maintenance of responsiveness to insulin. Reproduced by courtesy of "New York State Journal of Medicine."

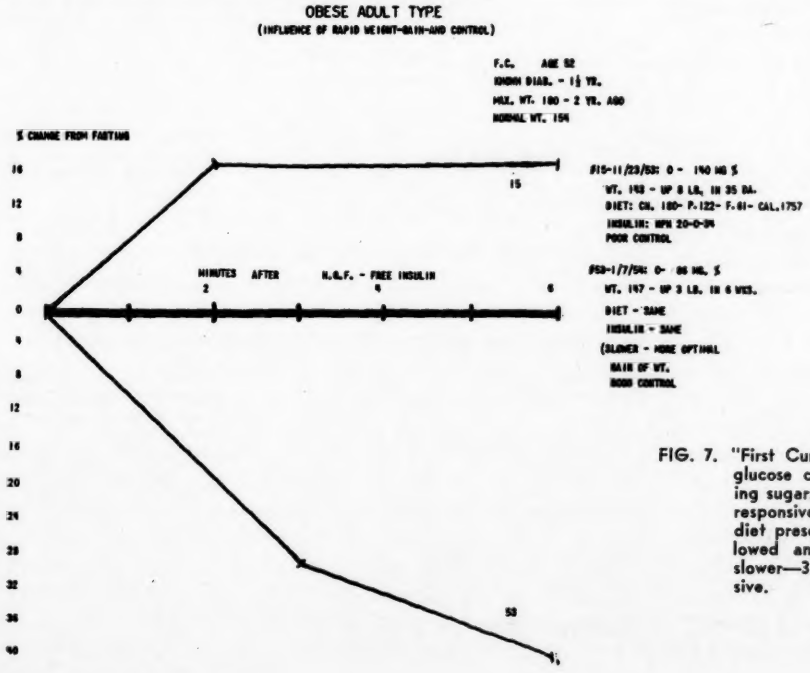
OBESE ADULT TYPE
(INFLUENCE OF RAPID WEIGHT-GAIN-AND CONTROL)
F.C. AGE 52
KNOWN DIAB. - 1½ YR.
MAX. WT. 180 - 2 YR. AGO
NORMAL WT. 154
% CHANGE FROM FASTING
MINUTES AFTER N.G.F. - FREE INSULIN
15
53
#15-11/23/53: 0 - 140 MG %
WT. 143 - UP 8 LB. IN 35 DA.
DIET: CH. 180- P.122- F.61- CAL.1757
INSULIN: NPH 20-0-24
POOR CONTROL
#53-1/7/54: 0- 86 MG. %
WT. 147 - UP 3 LB. IN 6 WKS.
DIET - SAME
INSULIN - SAME
(SLOWER - MORE OPTIMAL
GAIN OF WT.
GOOD CONTROL

FIG. 7. "First Curve" (No. 15). Patient under poor glucose control despite reasonably low fasting sugar. Had gained 8 lbs. in 35 days—unresponsive. Second Curve (No. 53) with diet prescribed same but conscientiously followed and insulin same—weight gain was slower—3 lbs. in 6 weeks. Now over-responsive.

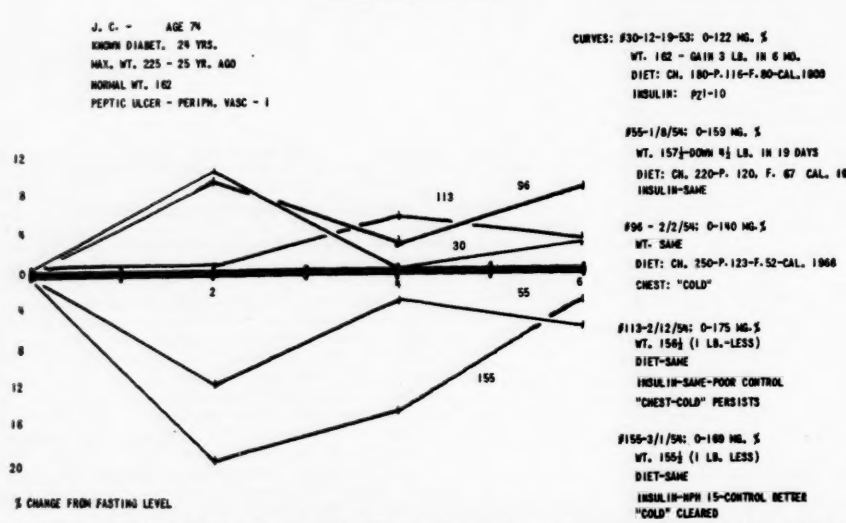


FIG. 8. "First curve" (No. 30), patient 74 years of age; known diabetic for 24 years. On insulin for 15 years. Fasting level—122 mg. per 100 cc. Unresponsive to insulin. "Second curve" (No. 55). Three weeks later: insulin same, but dietary carbohydrate raised. Patient now responsive to insulin. "Third and Fourth curves" (No. 96, 113). unresponsive despite elevation of dietary carbohydrate; chest "cold"; "Fifth curve" (No. 155). After recovery from chest "cold"; again responsive. Reproduced by courtesy of the "Brooklyn Hospital Journal."

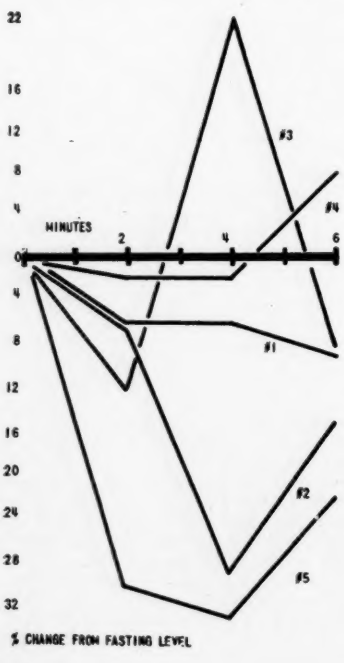


FIG. 9. Curve No. 1. Poor response shown; control poor on a diet too high in calories.
Curve No. 2. Better control on a diet lower in calories.
Curve No. 3. Control poor; anxiety over new job.
Curve No. 4. Control still poor; anxiety persists.
Curve No. 5. Adjusted to job; happy again; control good; normal responsiveness.
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TABLE 1

Findings in initial insulin responsiveness tests in 100 obese-adult diabetics (at random)

| | 59 patients 6%+ overweight at time of test | 25 patients normal in weight at time of test | 16 patients 6%+ underweight at time of test |
|---|---|---|---|
| Unresponsive or poorly responsive (59) | 11 T*<br>22 NT<br>33 | 2 T<br>10 NT<br>12 | 5 T<br>9 NT<br>14 |
| Normally responsive (27) | 14 T*<br>2 NT<br>16 | 9 T<br>1 NT<br>10 | 1 T |
| Over-responsive (14) | 9 T*<br>1 NT<br>10 | 3 T | 1 T |

*T=Adequately treated at time of first test.
NT=Untreated or inadequately treated at time of first test.
Summary:

1. Of 59 overweight diabetics tested, 34 had been adequately treated.* Of these, 23 (67%) were responsive after treatment.
2. Of 25 normal weight diabetics tested, 14 had been adequately treated. Of these, 12 (85%) were responsive after treatment.
3. Of 16 underweight diabetics tested, 7 had been adequately treated; 5 of these were unresponsive (unexplained).
4. Of the total 55 obese-adult diabetics adequately treated, 37 (67%) were responsive after treatment.
5. Four untreated patients were, nevertheless, responsive. Three of these were overweight (27, 32, and 33%, respectively).

*Adequately treated for glycosuria and glycemia but still 6 to 49% overweight.

TABLE 2

Analysis of 46 patients serially and successively tested over a period of 2 to 24 weeks (29 obese-adult type, A, and 17 juvenile type, J)

Of 29 A cases originally poorly or nonresponsive:
- 20 (77%) showed improved responsiveness after adequate treatment.
- 2 had been over-responsive before treatment (unexplained).
- 1 was normally responsive before treatment—liver pathology.
- 1 was unresponsive after treatment—hypertension.
- 1 was unresponsive after treatment—hyperthyroid.
- 1 was unresponsive after treatment—cardiac infarct.
- 1 was unresponsive after treatment (low fasting level).
- 2 were unresponsive after treatment (unexplained). 6 and 12% underweight, respectively.

Of 17 J cases:
- 2 were over-responsive before any treatment. Of the remaining 15 poorly or non-responsive patients:
- 10 (66%) showed improved responsiveness after adequate treatment.
- 2 were unresponsive (had remained on "free diet" and were still overweight).
- 1 was unresponsive (infection).
- 2 were unresponsive (unexplained). (7 and 31% underweight, respectively.)

from fatigue of the intrinsic mechanism occasioned by a prolonged and unrelenting hyperglycemia. One may aptly liken the role of long-persisting hyperglycemia to excessive stimulation by a galvanic current of a frog muscle preparation. Such stimulation ultimately leads to a refractory state in the muscle. Similarly, hyperglycemia ceases to act as a normal effective stimulus after long continued exposition. If, however, the spell of hyperglycemia is broken by mild caloric restriction, with or without insulin, stimulation of the native insulin mechanism by ingested carbohydrate again usually becomes possible.

The amount of ingested carbohydrate adequate[20-21] to act as a stimulus is in the diabetic individual usually over 150 gm. per day. Whereas in the nondiabetic 100 gm. or less in the course of a day acts as an effective stimulus, in most diabetics, whose insulin mechanism is usually notoriously sluggish, such relatively small amounts of carbohydrate are frequently ineffective as a stimulus. A daily carbohydrate moiety of over 150 gm. is in most instances stimulating, provided there are recovery phases from the hyperglycemia and provided that the total caloric ingestion is at or near the minimum basal needs for that individual (somewhere in the neighborhood of 25 calories per kilogram at the patient's ideal weight). Then, as the carbohydrate of the diet is stepped up at the expense of the fat moiety (reducing the fat content of the diet in order to keep the caloric value constant), the individual usually regains his native ability to respond promptly to insulin.

Improvement in the test is registered by a prompter fall in blood glucose as well as by an increased degree of fall in the six-minute period. Infection (figure 8), anxiety (figure 9), the regaining of excessive body weight, or too rapid gain of weight even in the underweight individual, (figure 7), will break glucose control and, to an equal degree, will cause a reversion of the curves to the unresponsive or poorly responsive type.

The so-called "brittle" or labile type of diabetic shows bizarre, exaggerated, and unexplained precipitous rises[13] and falls in blood glucose during the six-minute period of the test. These patients are obviously over-responsive to insulin and to the stimulus of ingested carbohydrate.

They should, accordingly, usually not be overindulged in dietary carbohydrate, lest with their ever-increasing ability to respond to the stimulus of ingested carbohydrate their "brittleness" become aggravated. We believe that brittle cases are often "physician-made," as a result of excessive dietary prescription of carbohydrate. These patients should perhaps be given only sufficient carbohydrate to stimulate their own insulin mechanisms (rarely over 180 gm. daily). They furnish good examples of a state in which overstimulation of an over-responsive mechanism plays havoc in the patient.

## CONCLUSIONS

1. It is possible to rehabilitate intrinsic insulin function in many diabetics by therapeutic application of well proved physiologic principles.

2. Depression of the intrinsic insulin mechanism by attrition or suppression should give way to a calculated effort at salvaging what may be left of the native insulinogenic mechanism.

3. Ingested carbohydrate is the sensitizing as well as the normal stimulating factor to the individual's own intrinsic insulinogenic mechanism.

4. Spot normal blood glucose determinations are not a satisfactory index of intrinsic improvement. A quantitative measure of improving ability to respond to insulin would carry much more significance.

5. That intrinsic insulin function does frequently improve by adequate conservative treatment is demonstrable by a simple laboratory procedure which measures the individual's ability to respond promptly to exogenous insulin, a six-minute test of responsiveness to glucagon-free insulin.

6. By the Six-minute Test of responsiveness to insulin diabetics can be classified clinically into three types: (a) those poorly responsive to glucagon-free insulin within the six-minute period, namely, the obese-adult type of diabetic before treatment, under inadequate treatment, or in the presence of infection, anxiety, or other factor breaking down insulin efficiency; (b) those responsive or over-responsive to insulin—the juvenile type of diabetic (at any age) when under even fair glucose control, and the obese-adult type of diabetic adequately controlled. With a resumption of poor glucose control, patients of both these types usually suffer a reversion to the type of curve originally found in (a); and (c) the labile or "brittle" type of diabetic, who shows bizarre, exaggerated precipitous changes in blood glucose within the six-minute period.

7. The test serves as a more delicate index of clinical improvement or regression than does the casual blood glucose determination.

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15 Anderson, G. E.: Glucagon-free insulin for insulin-sensitivity tests. Lancet *266*:979, 1954.

16 Anderson, G. E.: Six-minute responsiveness test to insulin. Science *119*:516, 1954.

17 Murlin, J. R., Clough, H. D., Gibbs, C. B. F., and Stokes, A. M.: J. Biol. Chem. *56*:252, 1923.

18 Somogyi, M.: Insulin administered intravenously in the postabsorptive state. J. Biol. Chem. *179*:217, 1949.

19 Anderson, E., Lindner, E., and Sutton, V.: Sensitive method for assay of insulin in blood. Am. J. Physiol. *149*:350, 1947.

20 Anderson, G. E.: Carbohydrate and fat metabolism. In Goldzieher and Goldzieher, Endocrine Treatment in General Practice. New York, Springer Publishing Co., p. 60, 1953.

21 Anderson, G. E.: Creed for treatment of diabetes. Am. J. Digest. Dis. *14*:170, 1947.

## DISCUSSION

E. PERRY MCCULLAGH, M.D., (*Cleveland*): Dr. Anderson has complimented me by asking me to discuss this paper, but I should like to make it clear at the beginning, that I have no experience whatever with this test myself. What I have to say is philosophical, if you wish, and simply an expression of the thoughts that come to mind as to what these data may mean or how important they may be.

It is recognized by all of us that there are many homeostatic mechanisms, that control the blood sugar level. Dr. Anderson has tried to avoid measuring the effects of epinephrine, glucagon or other factors within the patient by observing the effect of insulin quickly, directly before other effects are likely to come into play. He has checked his method and has satisfied himself that duplicate figures can be obtained with double tests of the same samples of blood.

He spoke very little, as you probably noticed, about the normal response. He is apparently not ready to define exactly what the normal response is. In approximately 80 tests on presumably normal students, the majority, at least, show a rapid and a rather marked fall in blood sugar level, but in quite a few cases after hypoglycemic levels are reached the blood sugar rises rapidly. One wonders whether this may not in itself be a glucagon effect even though he tries to avoid it. I grant that it is very fast. Glucagon does work rapidly. It depends, of course, on the state of the liver of the patient since glucagon must have liver glycogen on which to act. The curves just shown in the preceding paper would indicate that glucagon effect may be in ten minutes and perhaps a maximum of twenty or thirty minutes, so perhaps this is too fast since it reacts in four minutes.

Dr. Anderson seems to show that the change in response which follows treatment is actually due to the treatment, and with this I am inclined to agree. Whether it is due to the production of more insulin within the body is uncertain. He said that he believes this test indicates that by proper treatment the reactivity of the person, or his cells, to insulin is better. The mechanism by which such an effect is produced is certainly interesting and will be clarified, I hope, by further work.

I think that it may be worth while to emphasize Dr. Anderson's aim. He is striving to present a clearer explanation of the true physiological situation in the diabetic patient under varying degrees of control. It is to be hoped that this will be a step in the direction of eventual total rehabilitation of the diabetic.

# ABSTRACTS

Alonso, Patino M. (*'Calixto García' Hospital, Metabolic Unit, Habana, Cuba*): PRESENT TREATMENT OF DIABETES. Arch. Med. Int. *13*:235-45, Nov.-Dec. 1953.

Dietary regulation and insulin administration when necessary constitute the two main aspects of the treatment of diabetes. The author believes that the maintenance of normoglycemia and aglycosuria should always be the objective of therapy. (Spanish)

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Anderson, George E. (*State Univ. of New York Coll. of Med., New York, N. Y.*): GLUCAGON-FREE INSULIN FOR INSULIN-SENSITIVITY TESTS. Lancet *1*:979, May 8, 1954.

The author claims that observation of the blood sugar curve within the first six minutes after giving glucagon-free insulin intravenously in small doses (1 to 3 units) will show the immediate effect of insulin, before the fall in blood glucose can excite counter-measures. During the first six minutes, only those factors actually operating in the body at that particular time can prevent or delay the onset of hypoglycemia or reduce the rate of fall of blood glucose. Later other factors will modify the curve.

Several applications of the six-minute insulin-sensitivity test are proposed. The author believes that it can be used to differentiate clinical types of diabetes, to detect prediabetes, and to evaluate progress during treatment.

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Anderson, George E. (*Dept. of Med., State Univ. of New York Coll. of Med. at New York City, and the Brooklyn Hospital*): PRACTICAL METHOD OF REHABILITATION OF INSULIN FUNCTION IN DIABETES: THE SIX-MINUTE INSULIN RESPONSIVENESS TEST. New York State J. Med. *54*:2167-74, August 1, 1954.

By means of a six-minute insulin-responsiveness test utilizing glucagon-free insulin given by vein, the author has classified characteristic responses in two major types of diabetes. In a study of 272 blood sugar curves, he has found that adult diabetics with obesity before adequate therapy usually show poor responsiveness or non-responsiveness. A change to normal responsiveness has been observed in 80 per cent after adequate therapy, apparently indicating a rehabilitation of insulin function. In the case of juvenile diabetes, he has found normal or even excessive responsiveness to glucagon-free insulin. With proper dietary measures this overresponsiveness has frequently been stabilized.

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Appel, Saul B.; Gluck, Joseph L.; Schlecker, Austin A.; Miller, Alfred; Reichman, Stanley; Springer, Charlotte; Goldman, Abraham; Rosenbluth, Milton; and Kupperman, Herbert S. (*Third (N. Y. Univ.) Med. Div., Goldwater Memorial Hosp., and Dept. of Therapeutics, N. Y. Univ.-Bellevue Medical Center, New York, N. Y.*): THE COMPARATIVE EFFECT OF ADRENOCORTICOTROPHIC HORMONE EXTRACTS ON BLOOD GLUCOSE IN MAN. Acta endocrinol. *14*:99-107, Oct. 1953.

Comparable doses of the three corticotropin preparations standardized by the same assay method exhibited definite and yet distinct differences in producing elevation of the blood-fasting glucose before or after intravenous administration of glucose. Only two preparations displayed significant anti-insulin activity. These data support the concept of a multiplicity of biological activities of corticotropin preparations.

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Arias, Vallejo E. (*Madrid, Spain*): ON MAURIAC'S SYNDROME: DWARFISM, HEPATOMEGALIA AND OBESITY WITH JUVENILE DIABETES MELLITUS. Rev. españ. enferm. ap. digest. *13*:159-61, March-April 1954.

This syndrome characterized by dwarfism, hepatomegalia, and obesity in a diabetic child was first described by Mauriac in 1930. Hepatomegalia results from glycogen and fat deposition in the liver; dwarfism is the result of pituitary insufficiency secondary to poor nutritional state, and as a cause of the obesity, Mauriac mentions the hypersecretion of adrenal cortical hormones producing the moon-like face. Further experience and the better control of diabetes in these children with long-acting insulins has brought about new concepts in this presently rare syndrome. (Spanish)

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Aun, Yeoh Seang. THYROTOXICOSIS WITH DIABETES MELLITUS. Proc. of the Alumni Association, Malaya *6*:190-91, Sept. 1953.

As the carbohydrate tolerance is reduced in the majority of thyrotoxic patients, the diagnosis of diabetes mellitus

in association with hyperthyroidism has to be made cautiously. Nevertheless, the association of these two diseases is serious, since each accelerates the downward course of the other. Thyrotoxicosis may also unmask latent diabetes. The diabetic state is greatly improved with control of the hyperthyroidism.

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Beattie, J. (*Strangeways Res. Lab., Cambridge, Mass.*): Insulin Resistance Following Hypothalamic Lesions and Removal of the Adrenal Medulla. Brit. M. J. *1*:1287-90, June 5, 1954.

After section of the pathways from the hypothalamus to the brain stem and removal of the adrenal medulla, rats kept at an environmental temperature of 29.5° C. showed no fall in the blood-glucose level thirty minutes after the injection of insulin in a dose of 1 unit per kg. of body weight. Removal of the adrenal medulla alone or section of the hypothalamic pathways produced no change in insulin sensitivity. The resting content of glycogen in muscle (gastrocnemius) was significantly lower than normal in rats with the hypothalamic lesions and without adrenal medullary tissue. The glycogen content did not rise after the injection of glucose (1 mg. per gm. of body weight) or after the simultaneous injection of glucose and insulin. The glycogen content of the liver was markedly reduced (15 per cent of normal) in the resting state. When such rats were exposed to cold for nine days, they still displayed no hypoglycemic response to the injection of insulin. The glycogen content of the liver in the resting state was reduced to 11 mg. per 100 gm. of liver. The experimental data suggest that the insulin resistance found in these rats was due to the presence of an insulin antagonist.

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Bennett, Leslie L. (*Univ. of Calif. Sch. of Med., Berkeley, Calif.*): Experimental Studies of Diabetes Mellitus: Some Effects of Growth Hormone and of Pyridoxine or Pantothenic Acid Deficiency. Kaiser Foundation Medical Bulletin *1*:430-35, Oct.-Nov. 1953.

Pyridoxine deficiency does not appear to alter the severity of diabetes mellitus in the rat. In the same study it has been found that pyridoxine deficiency does not alter the carbohydrate-sparing effect of insulin, but partially inhibits the nitrogen-sparing effect of insulin. An early pantothenic-acid deficiency may be associated with some degree of insulin resistance; a late deficiency may be associated with some degree of insulin hypersensitivity. Growth hormone exerts an extra-pancreatic insulin antagonism. Evidence has been presented consistent with the conclusion that growth hormone may lead to an increased insulin secretion in both the dog and the rat.

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Bergqvist, Nils (*Med. Dept., Malmö Gen. Hosp., Sweden*): The Gonadal Function in Female Diabetics. Acta Endocrinol. *15* (Supplementum 19): 3-20, 1954.

A study has been made of some significant phenomena connected with the ovarian function in female diabetic patients of Malmö General Hospital. The menarche of 33 previously diabetic girls occurred at an age of 11.5 to 19.5 years (average 15.0 years). In 114 nondiabetic women the menses commenced at an age of 11 to 18 years (average 13.9 years). The difference of 1.1 years is highly significant. With regard to the nonbiologic factors which have a restraining effect on the frequency of pregnancy in diabetic women and also to the increased frequency of spontaneous and therapeutic early abortions in the diabetic women, statistics indicate that the actual biologic fertility has been but slightly impaired, if at all. On the whole it seems that the menopause occurs at a slightly lower age in diabetic women than in the comparative group of nondiabetic women employed.

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Bergqvist, Nils (*Med. Dept., Malmö Gen. Hosp., Sweden*): The Gonadal Function in Male Diabetics. Acta Endocrinol. *15* (Supplementum 18): 3-29, 1954.

Sixty-four male diabetics between 20 and 45 years of age have supplied information regarding their sexual libido and potency. Persistent lack of libido occurred in 11 cases, persistent impotence also in 11 cases; sometimes the two symptoms were concomitant, sometimes not. All except one were among the older patients, 33 to 45 years of age. There was often a dissociation between lack of libido and impotence; some patients complained of the former, others only of the latter. None of the two sexual symptoms was correlated to the duration of the disease, nor did the diabetic control seem to be poorer in these patients than in those without sexual symptoms. In men, 20 to 39 years of age, the 17-ketosteroid values were significantly lower in patients with an average glucosuria of more than 30 gm. per 24 hours than in a group with 0 to 30 gm. per 24 hours.

One group of patients which were examined both during relatively high as well as during slight glucosuria had significantly higher 17-ketosteroid values on the latter occasion. Poorly adjusted diabetics had significantly lower gonadotropin values than a group of normal individuals, while well-adjusted insulin-treated patients had gonadotropin values which agreed well with the normal figures. These observations probably indicate that the decreased 17-ketosteroid excretion in younger men—especially the inadequately insulin-treated—is due to a reduction in the hypophyseal gonadotropins.

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Bergstrand, C. G.; and Hellström, B. E. (*Pediat. Clin., Karolinska Institutet, Karolinska Sjukhuset, Stockholm, Sweden*): THE ONE-HOUR TWO-DOSE GLUCOSE TOLERANCE TEST IN NORMAL AND OBESE CHILDREN. Acta endocrinol. *14*:335-40, Dec. 1953.

The one-hour, two-dose glucose tolerance test was performed with 1 gm. of glucose per kg. of body weight in 86 children without any known metabolic disorders and in 46 obese children. When the former group of children was divided into two age groups, 1 to 7 years of age and 8 to 15 years of age, the mean fasting value was found to be significantly higher in the older group. This older group also showed higher 30-minute and 60-minute values. The glucose tolerance curves on 23 children without known metabolic disorders reached significantly higher values at 30 minutes when given 2 gm. of glucose per kg. of body weight than with 1 gm. of glucose per kg. of body weight. The 60-minute value was not significantly higher. All types of tolerance curves were obtained but the average curve in both normal and overweight children showed a blood-sugar value which was higher at 60 minutes than at 30 minutes. No difference in fasting values or glucose tolerance could be shown between the normal and the fat children.

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Blaisdell, E. R. (*Med. Serv., Maine Med. Center, Portland, Me.*): MEDICAL MANAGEMENT OF THE SURGICAL DIABETIC: A STATISTICAL ANALYSIS OF 500 PATIENTS. J. Maine M. A. *45*:214-17, August 1954.

The author presents data concerning 500 surgical diabetic patients. There has been a reduction in mortality rate from 16 per cent in 1935 to from 4 to 5 per cent in 1946. In his sixth series on which he is now working there have been no deaths in 60 cases treated. If 500 cases are sufficiently large in number to permit a definite conclusion, it can be said that any further decrease in mortality rate will depend upon improvement in the prevention and treatment of cardiovascular and kidney diseases.

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Boulet, P.; Mirouze, J.; and Fruteau de LaClos, C. (*Montpellier, France*): MIXTURE OF THREE INSULINS (REGULAR INSULIN, PROTAMINE-ZINC INSULIN, NPH) IN THE TREATMENT OF UNSTABLE AND RESISTANT INSULIN DIABETES. Presse Méd. *61*:1428-30, Nov. 4, 1953.

In unstable-insulin diabetes, insulin administration seems to be excessive, but the dosage should be sufficient to overcome completely the acido-ketosis without inducing serious hypoglycemia. In resistant-insulin diabetes, the response may be inadequate even with the highest dosage. The authors used a mixture of the three insulins in the same syringe given two hours before the midday meal. The most efficient proportions of NPH, regular insulin, and protamine zinc insulin seem to be 4, 2, 1, but these may be revised for each case. (French)

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Bowman, Walter M.; and Enterline, Philip E. (*Hyg. Lab. Div., W. Va. State Dept. of Health, Charleston, W. Va.*): DELAYED BLOOD SUGAR DETERMINATIONS: EVALUATION OF A BLOOD PRESERVATIVE. Pub. Health Rep. *69*:240-46, March 1954.

A series of experiments is presented to determine the value of the combination of 10 mg. of sodium fluoride and 1 mg. of thymol per ml. of whole blood in maintaining the glucose content of blood, under conditions which would be characteristic of a diabetes case-finding program, conducted in conjunction with blood-collection programs for venereal disease. For periods up to 96 hours, it was estimated that less than a third of the blood specimens actually changed in glucose content. These changes were small. They were about equally divided between increases and decreases in the glucose content of specimens and would probably be of little or no clinical significance in diabetes case-finding programs. The preservative was not considered satisfactory for periods beyond 96 hours.

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Bricker, Neal S. (*Res. and Devel. Branch, Fitzsimons Army Hosp., Denver, Col.*): DIABETES MELLITUS: CHANGING ETIOLOGIC CONSIDERATIONS. M. Times *82*:24-29, Jan. 1954.

Diabetes has been portrayed as a syndrome of varying origins and characteristics, exhibiting hyperglycemia, glycosuria, and deficient glycogen deposition. The theory that all diabetes is pancreatic in origin has been criticized and certain extrapancreatic factors have been explored for possible etiologic roles.

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Cardell, B. S. (*King's Coll. Hosp. Med. Sch., London, England*): THE INFANTS OF DIABETIC MOTHERS: A MORPHOLOGICAL STUDY. J. Obst. & Gynaec. Brit. Emp. *60*:834-53, Dec. 1953.

The abnormal findings at postmortem in 25 infants of diabetic mothers are reported and compared with those recorded in the literature. As a group these infants show certain characteristic features: They are larger than normal and the increase in weight parallels the increase in length. Despite their large size many of these infants are premature. With a few exceptions organ weight is proportional to body weight. The liver and spleen frequently show an increased degree of hemopoiesis. There is no increased hemosiderosis. The pancreas frequently shows an infiltration by eosinophils and an increase of islet tissue because of an increase of beta cells. Immature glomeruli are frequently found, supporting the contention that despite their large size many of these infants are premature. There appears to be a significant increase in the incidence of follicular ovarian cysts with luteinization of the theca interna. In the infants of mothers receiving hormone therapy there are occasional reports of genital abnormalities. Apart from an increase of size of the placenta no significant lesions have yet been described. The reason for the high fetal mortality and the abnormalities in the infants of diabetic mothers is unknown. Overactivity of the maternal anterior pituitary gland is an attractive theory but it is not yet supported by adequate evidence. It is possible that genetic factors may play some part.

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Cook, Marion H.; Free, Alfred H.; and Giordano, A. S. (*Miles-Ames Res. Lab., Elkhart; South Bend Med. Foundation, South Bend, Ind.*): THE ACCURACY OF URINE SUGAR TESTS. Am. J. M. Technol. *19*:283-90, Nov.-Dec. 1953.

A series of urine samples from hospital patients and from healthy subjects has been tested with Benedict's qualitative test and with Clinitest. Benedict's qualitative test is the more sensitive of the two tests for urine sugar, but this appears to be a disadvantage because many urine samples from healthy subjects give trace reactions with this test. In specimens of urine which contain sugar, Clinitest measurement of the quantity of sugar gives a good correlation with the amount of sugar determined with Benedict's quantitative method. Both Clinitest and Benedict's qualitative test are completely accurate when properly performed. Mistakes may be made with both methods but are less likely with Clinitest.

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Coste, P. Dalle, and Klinger, R.: USE OF MASSIVE DOSES (500 TO 1,000 MCG.) OF VITAMIN $B_{12}$ FOR VARIOUS CONDITIONS PRESENT IN DIABETIC PATIENTS. Policlinico (sez. prat.) *61*:143-49, Feb. 1, 1954. (Abstr. in J.A.M.A. *155*:781, June 19, 1954).

Vitamin $B_{12}$ was always well tolerated and never caused toxic effects. Good results were obtained in cases of diabetes with neurologic conditions including one case of herpes zoster. It is believed that in its physiological mechanism this vitamin uses as a catalytic agent some lipid complexes which are present in high concentration in the nervous sheaths. Gratifying results were also observed in two cases with pruritus vulvae. Changes in carbohydrate metabolism attributable to the vitamin were not observed. (Italian)

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Current Comment: GLUCAGON. M. J. Australia *2*:383, Sept. 5, 1953.

Much work is being done on the relations between insulin, glucagon, and growth hormone, and there is evidence that all these substances are concerned with growth. Glucagon has become an important factor in all considerations of the etiology of diabetes, and many of our concepts on the interrelationships between the endocrine glands will have to be revised in the light of the new knowledge which has accumulated.

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Dall 'Oglio, D.; Mantovanelli, S. (*Italy*): CLINICAL CONTRIBUTION TO THE STUDY OF THE EXTON-ROSE GLYCEMIC CURVE. Riforma med. *10*:259, 1954.

The authors believe that an Exton-Rose test should be done when it is difficult to carry out a standard test for the evaluation of carbohydrate tolerance. An evident disturbance in carbohydrate metabolism is shown when the third blood sugar value (one hour after the first dose

of 50 gm. of glucose, 30 minutes after the second 50 gm.) is greater than the fasting blood sugar and the second blood sugar value (30 minutes after the first 50 gm. of glucose). They consider that hyperglycemia without glycosuria would indicate a mild diabetes, whereas similar blood values accompanied by glycosuria would indicate moderate diabetes. (Italian)

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Daughaday, William H., and Larner, J. (*Depts. of Medicine and Biological Chemistry, Washington University Sch. of Med., St. Louis, Mo.*): THE RENAL EXCRETION OF INOSITOL BY NORMAL AND DIABETIC RATS. J. Clin. Investigation 33:1075-80, August 1954.

Depancreatized and alloxan diabetic rats excrete much more inositol in their urine than do normal rats. Although the inositol in the urine of normal rats is little influenced by dietary intake, that of diabetic rats is correlated directly with the amount of inositol ingested. It is concluded that the inosituria of diabetes mellitus can be attributed to an increase in the renal clearance of inositol produced by glycosuria.

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De Oya, J. C.; Jiménez Díaz, C.; and Grande, F. (*Dept. of Physiol., Univ. of Madrid, Madrid, Spain*): BLOOD SUGAR TOLERANCE TESTS IN VARIOUS TYPES OF EXPERIMENTAL DIABETES (CONTRIBUTION TO THE STUDY OF THE ROLE OF THE KIDNEY IN CARBOHYDRATE METABOLISM). Bulletin of the Institute for Medical Research, University of Madrid 4:207-14, Oct.-Dec. 1951.

A study is made of recuperation from hyperglycemia induced in animals which receive 1 gm. of glucose per kg. of body weight intravenously under varying conditions. Normal and nephrectomized dogs behave in the same way, but those with the pancreas removed show a decrease in the recuperation rate. The alloxan-diabetic dogs behave differently; hyperglycemia is more persistent and sometimes traces a di- or polynodal curve. Pancreatectomized dogs which also have the kidneys removed give results similar to the alloxan diabetic. These facts are taken to be further proof of the part played by the kidney in carbohydrate metabolism and by a lesion of the kidney in the origin of alloxan diabetes. In addition, its possible mechanism is discussed.

Eastland, J. Sheldon: SYMPOSIUM ON DIABETES: GENERAL MANAGEMENT. Maryland State M. J. 2:363-66, July 1953.

The author believes that the objectives of treatment of diabetes are best attained when the blood sugar level and glycosuria are strictly controlled. This is best accomplished by measured diets and insulin.

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Fabrykant, Maximilian (*Dept. of Med., N. Y. Univ. Post Graduate Med. Sch., New York, N. Y.*): THE ALPHA CELLS OF PANCREATIC ISLETS AND THE PATHOGENESIS OF DIABETES MELLITUS. Am. J. Digest. Dis. 20:275-77, Sept. 1953.

The author discusses some of the theories that have been advanced to explain the pathological physiology of diabetes. The function of the alpha cells in the production of the hyperglycemic-glycogenolytic hormone, glucagon, is discussed in relation to its effect on carbohydrate metabolism. The author also discusses Ferner's theory of the causation of diabetes and presents what is known of the physiology of the alpha cells.

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Fall, Harold F. (*Dept. of Ophth., Univ. of Mich. Med. Sch., Ann Arbor, Mich.*): CLINICAL DETECTION OF THE GENETIC CARRIER STATE IN OPHTHALMIC PATHOLOGY. Am. J. Ophth. 37:841-54, June 1954.

Although diabetes mellitus has a genetic basis, it is not known if the ocular (that is, retinal and lenticular) complications of diabetes are genetically influenced.

The carrier state may occasionally be detected by abnormal glucose tolerance curves. In a patient prepared by special diet, there is some evidence to suggest that the administration of cortisone 12 to 24 hours prior to a glucose tolerance test may make more certain the detection of the carrier individual. (See Fajans and Conn, DIABETES 3:296-304, July-August 1954.

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Feldman, Maurice; and Feldman, Maurice, Jr. (*Sinai Hospital, Baltimore, Md.*): THE ASSOCIATION OF CORONARY OCCLUSION AND INFARCTION WITH DIABETES MELLITUS: A NECROPSY STUDY. Am. J. M. Sc. 228: 53-56, July 1954.

In 1319 consecutive adult necropsies, the authors report a 10.4 per cent incidence of diabetes. Among the 137 cases of diabetes, the incidence of associated coronary

occlusion and infarction was 43.8 per cent as compared with a corresponding incidence of 20.1 per cent in non-diabetic adult cases. In diabetics, both with and without associated coronary occlusions, females predominated, with a respective incidence of 60 and 61 per cent. By contrast, males predominate among patients with coronary disease but without diabetes.

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Filho, Salgado (*Rio de Janeiro, Brazil*): TREATMENT OF DIABETES. Rev. brasil. med. *11*:50-51, Jan. 1954.

Several comments are made concerning a case of benign diabetes. Eighty per cent of the diabetic patients seen by the author are considered benign cases that do not require insulin administration, but only diet restriction. In the diagnosis of these cases a diet restricted in carbohydrate is advised while daily estimation of urinary volume and glycosuria is made for 8 to 10 days. A disappearance of glycosuria and a return to normal of urinary volume are good evidence that no need for insulin is present. If glycosuria and hyperglycemia remain unaltered, the use of insulin is imperative. (Portuguese)

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Fodden, John H. (*Dept. of Path., Sch. of Med. Sciences, Vermillion, S. Dak.*): ADDITIONAL CONCEPTS IN DIABETES MELLITUS. South Dakota J. Med. & Pharm. 7:59-63, March 1954.

Clear and accumulating evidence is outlining a role for the alpha cell of the pancreatic islet tissue in carbohydrate metabolism. This cell is charged with the production of a hyperglycemic factor, with a focus of biochemical activity upon the phosphorylase conversion of hepatic glycogen to glucose. There are reasons which suggest the regulation of its production by an anterior pituitary tropic hormone. However, concise definition of this substance as a hormone has yet to come, but is anticipated. It is believed that extraction technics, when perfected, may reveal its presence in circulating blood. If this is so, work will be stimulated to explore its participation in human diabetic metabolism, and especially the beliefs that familiar aberrances in the clinical sphere of this condition are referrable to the hyperglycemic factor.

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Franckson, J. R. M.; Gepts, W.; Bastenie, P. A.; Conard, V.; Cordier, N.; and Kovacs, L. (*Med. Clin., Brugmann Hosp., Univ. of Brussels, Belgium*): OBSERVATIONS ON EXPERIMENTAL STEROID DIABETES IN THE RAT. Acta Endocrinol. *14*:153-69, Oct. 1953.

Seventy rats, weighing about 200 gm., fed a diet containing 4 gm. of carbohydrates per day, were injected with 5 or 10 mg. cortisone daily for nearly one month. Cortisone administration was followed by a transitory diabetes, characterized by rising glycemia, lessened glucose tolerance and marked resistance to insulin. In 14 cases, cortisone induced glycosuria. Though the loss of weight was important, ureal catabolism was not strikingly increased. The most likely explanation of the rat-steroid diabetes seems to be reduced glucose utilization, due to inhibition of insulin activity by cortisone.

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Friedenwald, Jonas S. (*Baltimore*): DIABETIC RETINOPATHY. Am. J. Ophth. 37:953-59, June 1954. (New England Ophthalmological Society Proceedings).

The author reviews the nature of capillary aneurysms and their relationship to the Kimmelstiel-Wilson nodules often found in the kidneys of diabetics. Clinical and experimental reports are cited indicating that many diabetics have increased adrenal activity which may cause the microaneurysms in the retina and Kimmelstiel-Wilson nodules in the kidneys.

The frequent occurrence of neuritis in diabetics and the higher incidence of retinopathy in diabetics with neuritis suggests that vitamin deficiency may play a part in both. Experimental evidence indicates that increased adrenal function prevents the storage of vitamin $B_{12}$ in its normal fashion and that $B_{12}$ deficiency increases the effect of cortisone on the kidney.

A series of 24 patients with diabetic retinopathy was reported in which testosterone and vitamin $B_{12}$ were given for about four months. Three had exacerbations of their retinopathy in spite of treatment. Approximately half of the remainder showed no change and the other half showed no improvement. These results were not considered conclusive.

The author believes that control of diabetes helps give protection against retinopathy. There are 15 to 20 per cent of diabetic patients who are free from retinal lesions after 20 to 25 years of diabetes.

The capillary aneurysms, though they may be enormously exacerbated by the incidence of superimposed arteriosclerosis and hypertensive disease, are not in themselves directly the consequence of the hypertensive disease. It is suggested that perhaps the progress of renal

damage that occurs as a result of the Kimmelstiel-Wilson lesions in the glomeruli ultimately causes hypertensive disease.

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From, Paul (*Dept. of Internal Med., V.A. Hosp., Des Moines, Ia.*): CURRENT CONCEPTS OF CARBOHYDRATE METABOLISM AND DIABETIC ACIDOSIS. J. Iowa M. Soc. 44:421-27, September 1954.

The ingestion of carbohydrate substances leads to many varied and complex reactions resulting finally in the release of energy for work or the storage of potential energy in the form of glycogen. The Krebs tricarboxylic acid cycle, the Embden-Meyerhof cycle, etc., are part of these profound changes. Insulin acts also in this cycle of changes, probably at the hexokinase level and in a manner which is not too certain at the present time. The function of insulin is fourfold. One, it helps transform glucose to glycogen; two, it helps the tissues to oxidize glucose to carbon dioxide and water; third, it greatly enhances the transformation of glucose to fat; and fourth, it acts in the synthesis of protein from amino acids. It may be that insulin acts in the tricarboxylic acid cycle, in some fashion as yet unknown. Many hormones also act in this metabolism of carbohydrates. Somatotropin, corticotropin, adrenalin and thyroxin are a few. Neural control of this metabolism is mediated through the sympathetic and the parasympathetic nervous systems. Certain chemicals also exert an influence on these mechanisms such as alloxan and phloridzin.

When the utilization of carbohydrates is impaired, as in diabetes, the body stores of fat and protein are subjected to greatly increased demands. This may result in the accumulation of various toxic substances in the body which lead to acidosis and ketosis. The basic metabolic rate increases, resulting in dehydration, central shock with decreased peripheral resistance, hypotension, and increased cardiac output. The decreased utilization of glucose to oxygen by the brain results often in coma, but the mechanism of this phenomenon is not well understood. Also, at some time before or during the treatment of diabetic acidosis, most of the body electrolytes are reduced, sometimes to a marked degree, and they may require replacement.

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Gans, B.: DIABETES MELLITUS IN AN INFANT AGED 39 DAYS. Proc. Roy. Soc. Med. 47:132, Feb. 1954.

An infant was admitted to hospital 39 days after birth suffering from diabetic acidosis. The child weighed 5½ lb. at birth, was breast-fed, and was reported as always being hungry. He made good progress until two days before admission, when he refused his feedings and became irritable. On admission, he was semiconscious, grossly dehydrated, and cyanosed. He was placed in an oxygen box and given an antibiotic. A subcutaneous ("Hyalase") infusion of Hartmann's solution was begun. Next day his hydration was satisfactory, but he appeared even more desperately ill. The infusion was discontinued, and four hours later he was again severely dehydrated. This rapid dehydration, and a strong smell of acetone in the baby's breath, led to a blood sugar estimation. The result was 1,376 mg. per 100 cc.

After the first twenty-four hours 5 units of soluble insulin were injected before each four-hourly feeding. In spite of hourly urine testing and twice daily blood sugar estimations, perfect biochemical control proved impossible, but the baby appeared very well, and took his feedings avidly, even with blood sugar levels of 400 mg. per 100 cc. After six weeks of four-hourly injections of soluble insulin a change was made to one daily injection of 26 units insulin zinc suspension (lente). A single daily injection proved unsatisfactory, but the diabetes is now well controlled with two daily injections of 13 units of this long-acting insulin.

There is no evidence of cataract hypertension or retinal arteriosclerosis, but he has a well-marked subcutaneous fat atrophy of his right thigh. This first appeared after four weeks of treatment, an uncommonly early onset as it does not usually occur until some six months after the start of injections.

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Goodman, Joseph I. (*Cleveland Hts., Ohio*): VASCULAR LESIONS IN DIABETES MELLITUS. III. (PATHOGENESIS.) A.M.A. Arch. Ophth. 52:108-120 July 1954.

Diabetic retinopathy is a separate, discrete, readily recognized entity unrelated to atherosclerosis. Diabetic retinopathy and Kimmelstiel-Wilson disease are closely related anatomically and physiologically. In diabetics, the control of the diabetes is an important factor governing the devolpment of retinopathy and intercapillary glomerulosclerosis. Diabetic retinopathy is reversible. The retinal and glomerular lesions can be produced experimentally in rabbits with alloxan-induced diabetes by the administration of cortisone and corticotropin. Diabetic patients showing Kimmelstiel-Wilson lesions in the kid-

neys present in a high percentage of the cases lipid vacuoles in the zona fasciculata of the adrenal glands. Most likely retinopathy is a consequence of a metabolic disorder characterized by an hormonal imbalance. The concept of adrenal hyperactivity to explain the occurrences of retinopathy and intercapillary glomerulosclerosis in diabetics, though inviting, is still hypothetical and awaits confirmation.

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Goodman, Joseph I.; and Heller, Arnold (*Cleveland Heights, Ohio*): AN ANALYSIS OF INSULIN (HYPOGLYCEMIC) REACTIONS IN DIABETIC PATIENTS. I. STATISTICAL SURVEY OF 203 CASES. Am. J. Digest. Dis. *21*:9-12, Jan. 1954.

The authors present an analysis of 203 diabetics taking insulin. Insulin reactions were tabulated as to their character, severity, time of day and type of insulin used. Thirty-eight per cent of the cases gave a history of one or more reactions. Sixty-two of the 203 cases taking insulin when first seen were ultimately controlled on diet alone. Twenty-two per cent of this group had had insulin reactions. The seven most commonly used insulin preparations and the number of patients having reactions in each of these groups is tabulated. Of all the patients having reactions 74 per cent were taking the protamine group, 19 per cent took regular insulin and 7 per cent globulin. Of the group having severe reactions 81 per cent were on protamine insulin or mixtures containing protamine insulin. The incidence of reactions in severe diabetics was twice as high as in mild diabetics.

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Grande, F.: THE PHYSIOLOGICAL ROLE OF ZINC AND ITS RELATIONS WITH CARBOHYDRATE METABOLISM. Rev. Espan. Enf. Del Ap. Dig. Nutr. *12*:433, Sept.-Oct., 1953 (Abst. in Am. J. Digest. Dis. *21*:201, July 1954).

There is a lack of positive arguments to the role that zinc plays in carbohydrate metabolism. It is shown that present day knowledge has altered somewhat the interpretations of many facts found in medical literature. There is no definite proof that zinc is a necessary part of the insulin molecule; however, insulin can act without zinc being present. The pancreas has an abundance of zinc, but it has no relation to the exocrine activity of the gland, since there is no concentration of the metal in the island of Langerhans, but there is proof of its presence in the acinus cells. The author tells of his experimentation on animals and further discusses the reasons for his statement that one has no definite proof that zinc is necessary to the formation of insulin just, as he says, there is no definite proof that alloxan plays a physiological part in the regulation of the production of insulin.

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Grant, Joseph L. (*Med. Serv., V. A. Hosp., White River Junction, Vt.*): ELEVATED GLUCOSE THRESHOLD IN KIMMELSTIEL-WILSON SYNDROME. New England J. Med. *251*:302-04, August 19, 1954.

A group of ten patients with Kimmelstiel-Wilson syndrome is described. These patients averaged sixty years of age at death, and had had their diabetes for approximately twice as long as a comparable series of diabetic patients without intercapillary glomerulosclerosis. The clinical course in two cases is described, and it is shown that a characteristic feature of the group appears to be an increase in the renal threshold for glucose. This results from a decrease in renal plasma flow and glomerular filtration rate. It may result in unrecognized hyperglycemia if patients are followed only by tests for glycosuria.

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Guild, Harriet G.: JUVENILE DIABETES. Maryland State M. J. *2*:366-68, July 1953.

The management of diabetes in the child is an educational process starting with the onset of the disease and continuing until the child reaches full adulthood. It concerns not only the teaching of the facts of diabetes with regard to diet and insulin, but even more, the guidance and training of a human being to a certain way of life. This educational process has as its goal the production of a normal well-adjusted individual who has learned to live with a disease that is always with him and to handle it intelligently in a way that permits smooth sailing but at the same time allows a minimum of inconvenience. Since the vascular complications seem to be less frequent and less severe in those in whom good control has been consistently maintained, it involves also the acceptance of the importance of careful regulation.

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Hanske, W.: PROGRESS IN THE INSULIN FIELD. Die Pharmazie *9*:11-15, Jan. 1954.

Technics for the determination of the amino acid se-

quence of insulin are described, and recent work on the subject is reviewed. (German)

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Heintzelmann, Franz (*Centralsygehuset, Slagelse, Denmark*): LIVER FUNCTION IN DIABETES. Nor. med. *51*: 566-71, April 22, 1954.

In diabetics, hypoalbuminemia and hyperglobulinemia and elevation of the alkaline phosphatases are often found; but they must be regarded as nonspecific and not as a result of liver dysfunction. (Danish)

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Hollander, William; and Entwistle, George (*Boston Univ. Sch. of Med., Boston, Mass.*): LABILE DIABETES IN AN ELDERLY PATIENT WITH HYPERTHYROIDISM: A CASE REPORT. Boston Medical Quarterly *5*:19-25, March 1954.

A case of labile diabetes with complicating thyrotoxicosis is presented. A juvenile type of diabetes in an adult should arouse suspicion of complicating thyrotoxicosis.

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Jones, Benjamin F.: DIABETIC EMERGENCIES; PRE-AND POSTOPERATIVE TREATMENT. Maryland State M. J. *2*:368-74, July 1953.

In these days of crowded hospitals and operating-room schedules, an adequate period of preoperative care is often difficult or impossible to arrange. In the case of diabetics, however, it pays heavy dividends in better tolerance to surgery, and in superior results of surgery, to say nothing of shortened convalescence time. Certain types of preparation can be done in the home. An attempt should be made to reduce the weight in obese patients, and often this is unusually successful when they face the prospect of operation. The value of rest and supportive care for a generous period of time is strikingly seen in the case of diabetic patients in the older age group and in those with hypertensive cardiovascular disease, malnutrition, and general debility.

All diabetics scheduled for elective or nonemergency surgery should be admitted to the hospital in time for routine diagnostic procedures. Emergency operations on the diabetic can be carried out, if the patient is not in ketosis. Special care in following these patients should be exercised when their cases are unfamiliar to the attending physicians, or the diabetes has been previously unrecognized. The diabetic in ketosis or coma should have vigorous treatment, while operation is postponed, till acidosis and dehydration are corrected. Antibiotics, blood transfusions, and other measures may be needed to offset the delay. Ether anesthesia should be avoided in emergency cases. The preferred anesthetic for a diabetic is the one producing the least disturbance of carbohydrate metabolism and the acid-base balance. Local or regional block anesthesia and spinal anesthesia thus should be preferred over general anesthesia. Minimal doses of morphia preoperatively have been advised in diabetes because of the danger of anoxia. In the author's experience the tolerance of diabetics to the drug is not significantly less than that of nondiabetics. Operations upon diabetics should be scheduled at an early hour in the morning. Whatever the hour of operation the patient should receive an injection of insulin before operation, not later than the customary time for taking insulin. This preoperative insulin should be given in the form of protamine zinc, because of the stabilizing effect of its prolonged action. Judicious use of protamine zinc insulin may greatly facilitate negotiation of the crisis of operation.

In some cases, the problem of postoperative care becomes extremely complicated. This is particularly apt to occur when there is much impairment of renal function, emesis or diarrhea, and when the operation involves the gastrointestinal tract extensively, necessitating prolonged periods of total intravenous feeding. The removal of gastrointestinal fluid by suction also produces complex difficulties in diabetic postoperative management. In general, when nutrition is entirely or mostly by the intravenous route for a period longer than three days, it is necessary to add protein hydrolysates and soluble vitamins to the infusion fluids. When patients exhibit unexplained ketosis postoperatively, search should be made for infection. Sometimes the onset of ketosis heralds the fact that amputation of a toe has been unsuccessful in stopping the progress of atrophy and infection. When ketosis sets in after patients have resumed oral feedings, inadequate intake of carbohydrate is to be suspected, and the ketosis should be vigorously treated with additional regular insulin and forcing of carbohydrate by mouth or vein. Conversely patients who have been relieved of gangrenous and infected tissue by operation, may rather suddenly pass into hypoglycemia in the days just after the operation. In one such case, the patient was able to discontinue the use of insulin postoperatively although taking about 60 units daily before the operation.

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Jonxis, J. H. P.; and Huisman, T. H. J. (*Children's Hosp., the University of Groningen, The Netherlands*):

THE EXCRETION OF SUGARS AFTER THE INTRAVENOUS ADMINISTRATION OF INVERT SUGAR. Arch. Dis. Childhood. 28:466-49, Dec. 1953.

The authors studied the excretion of fluid and carbohydrates in a number of children who for 24 hours received either 10 per cent glucose or 10 per cent invert sugar. These children had been admitted to hospital for some acute infectious disease, and, as they showed signs of shock, they were given an intravenous infusion. The losses of invert sugar are 12.5 per cent of the glucose given and 1.5 per cent of the fructose. This shows that the loss of fructose is very small. It is remarkable that fructose increases the loss of glucose. However, during administration of 5 per cent glucose the loss amounted to 6.4 per cent; this rose after the addition of 5 per cent fructose to 12.5 per cent, double the amount. Also remarkable is the small output of urine after the administration of invert sugar, namely 768 ml. as against 1,127 ml. after the administration of 10 per cent glucose. Apparently fructose in some way or other retains fluid. This shows that the metabolism of fructose is not altogether similar to that of glucose. Since patients who need intravenous alimentation generally suffer from dehydration, this tendency of invert sugar to reduce diuresis is of practical importance. In view of the tendency to reduce diuresis and the rapid utilization of fructose by the cell, the authors consider invert sugar to be more suitable for intravenous administration than glucose of the same concentration, particularly if the concentration exceeds 5 per cent.

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Kalant, N. (*McGill Univ. Clin., Royal Victoria Hosp., Montreal, Canada*): METABOLIC EFFECTS OF THE PANCREATIC HYPERGLYCEMIC FACTOR. Proc. Soc. Exper. Biol. & Med. 86:617-19, July 1954.

Purified pancreatic hyperglycemic factor (HGF) was given to normal rats during a period of fasting or at the end of such a period. In the latter case HGF caused a fall in the level of ketonemia, which had developed as a result of the fast, but did not affect the blood sugar. When given during the fast, HGF greatly inhibited the development of ketonemia, increased the nitrogen excretion, and inhibited to some degree the rise in liver fat; it did not affect the liver glycogen or the blood sugar. These effects differ from those of adrenal hormones and of growth hormone. It appears that HGF is capable of playing an active part in fasting metabolism.

Keston, Albert S. (*New York University Coll. of Med., New York, N. Y.*): OCCURRENCE OF MUTAROTASE IN ANIMALS: ITS PROPOSED RELATIONSHIP TO TRANPORT AND REABSORPTION OF SUGARS AND INSULIN. Science 120:355-56, August 27, 1954.

The author reports that mutarotase occurs in kidney and liver but not in other tissues or blood plasma of hog, rabbit, chicken, rat, beef and lamb. D-xylose, d-galactose, arabinose, and d-glucose were found to be substrates of rat kidney mutarotase. L-rhamnose, d-mannose, and d-arabinose were not affected; sorbitol, mannitol, sucrose, and raffinose cannot mutarotate and were unaffected. Phlorizin (0.9 mg. per cc.) strongly inhibited (about 90 per cent) all substrates.

The author points out that the sugars acted upon by the enzyme as well as those not affected correspond precisely with the sugars which Homer Smith reported to be "actively" reabsorbed by the kidney and W. C. Stadie cited to be transported across cell membranes in response to insulin. Further, phlorizin inhibits mutarotase at concentrations found in kidney in "phlorizinized" animals. Based on the above facts, the author presents a unitary theory of sugar transport whereby mutarotase in kidney catalyzes interconversion of various forms of sugar toward the equilibrium mixture of a preferentially absorbed form (PAF) during passage of the filtrate down the tubules. This PAF sugar, whose formation is in the direction toward equilibrium and hence exergonic can be reabsorbed by the tubules into the blood without energy expenditure and is removed from the blood by transport across cell membranes under the influence of insulin.

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Lockhart, Jean D.; and Roboz, Elizabeth (*Dept. of Pediat. and Biochem., Georgetown Univ. Med. Sch., Washington, D. C.*): CASE OF GALACTOSEMIA IDENTIFIED IN A FOUR-DAY OLD INFANT BY PAPER CHROMATOGRAPHIC TECHNIC. Pediatrics 13:211-17, March 1954.

Galactosemia was diagnosed in a four-day-old girl by identification of sugar in the urine as galactose, using paper chromatographic technic. The child was placed immediately on a lactose-free formula, after which the urine became sugar-free and protein-free. Since the infant was fed only for a short time on lactose-containing formula, prognosis may be considered good. Details of the laboratory technic used in the identification of urinary galactose are presented. It is suggested that, by examina-

tion of the amniotic fluid of women in whose offspring galactosemia may be suspected because of a positive family history, a diagnosis might be made at birth, and then the baby never would be given a lactose formula.

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Martin, M. Mencer (*King's Coll. Hosp. London, England*): NEUROPATHIC LESIONS OF THE FEET IN DIABETES MELLITUS. Proc. Roy. Soc. Med. *47*:139-40, Feb. 1954.

The most important principle in surgery of the diabetic neuropathic foot in the presence of sepsis is never to close a wound but to leave the area wide open. Secondary suture is often possible a week or so later. Primary sutures frequently break down with spread of sepsis which necessitates longer hospitalization, often further surgery, and may even endanger the limb. With experience in the treatment of foot lesions in diabetics many more limbs can be saved which otherwise would come to grief.

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Mason, Percy (*122 E. 82nd St., New York, N. Y.*): SUICIDE IN ADOLESCENTS. Psychoanalyt. Rev. *41*:48-54, Jan. 1954.

Three patients were diabetics and used this organic illness—consciously and unconsciously—to express their self-destructive drives. These patients knew well the serious consequences of transgressions of diet or omission of insulin. It may have been the easiest tool available. On the other hand, these patients also knew that both insulin shock and diabetic coma are amenable to treatment and that there is a certain margin of safety offered to the patient, the family and the physician, in which they can come to the rescue and succeed. Could this be giving the environment a chance to save them, and to redeem itself, to become loving, accepting and understanding? Here the conflict between the conscious and unconscious wish to die and not to die may be at play so that these suicidal attempts are unsuccessful because of "faulty technic." These cases also illustrate the concept of partial suicide. The conscious and unconscious use of the diabetic condition in a repetitive manner as an expression of suicidal drives (it could facetiously be called suicide on the instalment plan) fits well into the concept of chronic suicide.

McCarty, W. Ross (*Dept. of Surgery, New York Univ. Coll. of Med., and the Third (New York Univ.) Surgical Division, Bellevue Hosp., New York, N. Y.*): THE ENZYMATIC-SURGICAL TREATMENT OF CHRONIC INFECTIONS OF THE FEET IN DIABETIC AND ARTERIOSCLEROTIC PATIENTS. S. Clin. North America *34*:415-21, April 1954.

The majority of the patients treated by the combined enzymatic-surgical method were in the sixth and seventh decades of life. Many had underlying diabetes and arteriosclerosis with impaired vascularity as etiologic factors in the infected ulcerative lesions. It would seem that when enzymes are utilized to remove the coagulums and purulent exudates, and surgery is used to remove the necrotic tissue and bone, then an improved approach has been made upon this problem.

Preoperative evaluation of the vascular supply to deep tissues is unsatisfactory. The presence or absence of pulsations and the degree of warmth of the foot do not delineate borderline circulatory conditions. Only at operation can a true evaluation of the status of the blood supply to the deep layers and muscles of the foot be obtained. If these tissues are edematous, avascular, and devitalized, the combined enzymatic-surgical approach is not attempted but amputation at a higher level is indicated. However, if a minimal blood supply is present, even though it is a surgical gamble the combined treatment is attempted, with the success indicated in the cases reported. Factors other than insufficient blood supply may be involved in chronic tissue damage in this type of patient, since the reversibility from disease to healthy tissue has been observed even though the vascularity appeared unchanged.

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Moldawer, Marc P.; Nardi, George L.; and Raker, John W. (*Dept. of Med. and Surgery, Harvard Med. Sch. and the Massachusetts General Hosp., Boston, Mass.*): CONCOMITANCE OF MULTIPLE ADENOMAS OF THE PARATHYROIDS AND PANCREATIC ISLETS WITH TUMOR OF THE PITUITARY: A SYNDROME WITH FAMILIAL INCIDENCE. Am. J. M. Sci. *228*:190-206, August 1954.

The authors review the literature and present a total of 28 cases of multiple endocrine tumors involving the pituitary, the parathyroids and the pancreatic islets. Clinical, operative or necropsy evidence implicated all three glands in twelve cases, the parathyroids and the pituitary in eight cases, the parathyroids and the pancreatic islets in six cases, and the pituitary and pancreatic islets in two cases.

Four cases of multiple endocrine tumors were found in the files of the Massachusetts General Hospital. Two cases of multiple parathyroid adenomas are presented in a father and daughter. In addition, the father had evidence of a pituitary tumor, and the daughter had hyperinsulinism and two islet cell adenomas of the pancreas. A third case, of acromegaly and hyperparathyroidism, is presented. In a fourth case, a minute parathyroid adenoma and a large islet cell tumor were found at necropsy without prior clinical evidence that either was functioning.

Because the family history frequently indicates involvement of one or more of the glands under consideration in other members, the authors suggest that there is no etiological relationship between these tumors, but that their coexistence is more likely due to undetermined genetic influences.

The likelihood of finding more than one parathyroid or pancreatic tumor in individuals known to have multiple endocrine adenomas is stressed. Fourteen of the twenty-six cases with parathyroid adenoma had multiple tumors. Twenty-five per cent of the cases had associated peptic ulcers.

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Murdoch, Robin (*Res. Dept., Glasgow Royal Maternity and Women's Hosp. Glasgow, Scotland*): HYPERGLYCAEMIA AND HAEMORRHAGIC SHOCK IN PREGNANCY: PRELIMINARY STUDY. J. Obst. & Gynaec. Brit. Emp. *60*:785-92, Dec. 1953.

Hemorrhagic shock, which may occur in various phases of pregnancy, produces hyperglycemia, and there is a definite relationship between the level of the blood sugar and the length of time which has elapsed between the onset of the shock and the taking of the sample.

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Muri, Jan (*Aker Hospital, Oslo, Norway*): DIABETIC NEPHROPATHY AND RETINOPATHY. Acta med. scandinav. *149*:211-19, August 1954.

The development of vascular complications in diabetics parallels in many ways the increasing problem of coronary diseases. The greater frequency in urban than in rural population is suggestive of harmful environmental influences. Freedom from the mental stress connected with life in big cities and highly industrialized areas may, to a certain degree, have protected the diabetics in this typical countryside of Norway from late diabetic complications, and more than offset the lack of control. It is doubtful what may be gained by burdening these patients with a rigid diabetic control.

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Nagasawa, Kakuma; Mitsuhashi, Ken-ichi; and Takase, Shinsaburô: INSULIN CONTENTS IN THE TUMORS OF LANGERHANS' ISLANDS OF MEN AND IN THE PANCREAS OF A PATIENT SUFFERING FROM CUSHING'S DISEASE. Bull. Hyg. Lab. *71*:12-19, Jan. 1953.

The authors hitherto investigated the insulin content of various animal tissues and found the highest insulin content per gram of tissue ever known is that of the tunny fish which has 225 units. The insulin content in the pancreatic tumor tissue of the patient with hyperinsulinism was high, more than 82 units, which is about 26-fold compared with that of normal pancreas tissue of the same patient having 3.2 units. That of the pancreas of a patient suffering from Cushing's disease was low, being 0.75 units. (Japanese)

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Palumbo, Leonard (*Dept. of Obstet. & Gynec., Univ. of N. C. Med. Sch., Chapel Hill, N. C.*): DIABETES MELLITUS COMPLICATED BY PREGNANCY: A PRELIMINARY REPORT. North Carolina M. J. *15*:120-23, March 1954.

In a group of 50 viable pregnancies, 34 per cent of the patients received hormone therapy; 94 per cent of the patients were delivered by the vaginal route; the uncorrected fetal salvage was 74 per cent; the corrected fetal salvage was 80.3 per cent. It is not inconceivable that the obstetric objectives of a negligible maternal mortality and a higher fetal salvage in the pregnant diabetic are compatible with a normal, or only slightly increased, incidence of cesarean section.

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Pedersen, Jørgen (*Lying-in Dept. B, Rigshospitalet, Copenhagen, Denmark*): FOETAL MORTALITY IN DIABETICS IN RELATION TO MANAGEMENT DURING THE LATTER PART OF PREGNANCY. Acta endocrinol. *15*:282-94, March 1954.

Lying-in Department B, Rigshospitalet, Copenhagen, is a large department receiving, without any selection, patients with complications as well as many emergency cases. During the years 1926-1945 a total of 156 diabetic pregnancies were observed (old series). The fetal mortality for a birth weight of 1000 gm. and over was 38

per cent. During the years 1946-1952 a total of 149 diabetic pregnancies was observed (new series). The fetal mortality was 27 per cent. This new series is divided into two groups: long-term and short-term treated cases, according to the stage of pregnancy at which the patient was first seen. In 93 pregnancies with short-term management (94 babies) the fetal mortality was 36 per cent, in 56 cases with long-term (58 babies) 12 per cent.

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Pedersen, Jørgen (*Lying-in Dept. B, Rigshospitalet, Copenhagen*): GLUCOSE CONTENT OF THE AMNIOTIC FLUID IN DIABETIC PREGNANCIES: CORRELATIONS WITH THE MATERNAL BLOOD SUGAR. Acta endocrinol. *15*: 342-50, April 1954.

Twenty-nine values for the glucose concentration in the amniotic fluid were determined by the Hagedorn-Jensen method in 23 nondiabetic cases near term. The mean was 32 mg. per cent with a range of 10 to 61 mg. per cent. In 42 values from 34 diabetic cases the mean was 61 mg. per cent with a range of 23-139 mg. per cent and thus significantly increased. The capillary blood sugar of the mother (and the fetus) at the moment of sampling the amniotic fluid has a positive correlation with the amniotic sugar in diabetic as well as in nondiabetic cases. No differences were found between long-term treated and short-term treated cases. The reduced formula equation of the regression line in diabetics and nondiabetics is given. The concentration of sugar in the amniotic fluid seems to be a direct product of fetal tissues. No direct relationship was found between the concentration of sugar in the fluid and its amount.

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Pedersen, Jørgen; and Jørgensen, Gunnar (*Lying-in Department B, Rigshospitalet, Copenhagen*): HYDRAMNIOS IN DIABETICS: AMOUNT OF AMNIOTIC FLUID IN RELATION TO TREATMENT. Acta endocrinol. *15*:333-41, April 1954.

One hundred forty-nine pregnant diabetics were treated during the latter part of pregnancy with the aim of keeping down the blood sugar. This was accomplished by diet and plenty of insulin. To combat toxemia, hydramnios, and edema, table salt was restricted, and the total amount of fluid was kept down. Hormones, mercurial preparations, and ammonium chloride were never used. The incidence of hydramnios was 50 per cent (> fluid in excess of 1000 ml.) or 20 per cent (> fluid in excess of 1500 ml.) as determined by the present rough method, consisting of puncture of the membranes with a catheter and collection of the fluid. The 149 diabetics were divided in two groups, long-term treated and short-term treated, according to the period of the first attendance during pregnancy. A significant difference is demonstrated in the amount of amniotic fluid between long-term and short-term cases. The amount of fluid was less in the long-term series. Thus the average was 928 ml. in long-term and 1454 ml. in short-term cases in a special series. It is probable that this difference is due to the different length of time of treatment in the two series, but it was not possible to demonstrate which part of the treatment was the most decisive in keeping down the amount of fluid. No correlations were found between hydramnios and diabetic retinitis, toxemia, fetal mortality, or birth weight (2600 to 5000 gm.).

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Pincus, I. J.; Hurwitz, J. J.; and Scott, M. E. (*Dept. of Physiology, The Jefferson Med. Coll., Philadelphia, Pa.*): EFFECT OF RATE OF INJECTION OF ALLOXAN ON DIABETES IN RABBITS. Proc. Soc. Exper. Biol. & Med. *86*:553-54, July 1954.

Alloxan doses of 75, 100, and 150 mg. per kg. were injected intravenously into rabbits, at three different rates: (1) less than one minute, (2) 5 to 20 minutes, and (3) between 30 and 50 minutes. When the alloxan in any of the doses employed was injected very rapidly, more than 50 per cent of the animals died. When the rate was very slow, about 50 per cent of the animals failed to show any evidence of diabetes. It appears that a rate of injection between these extremes is most satisfactory. When the alloxan was administered in a period of about 10 minutes, the largest number of surviving severely diabetic animals resulted.

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Pizon, P.: OSTEO-ARTHRITIC SYNDROME IN DIABETICS. Presse méd. *62*:1156, Aug. 14, 1954.

Out of 265 diabetics, 24 showed vertebral changes which fell into two categories. Osteoporosis was present in 12 cases, and hypertrophic arthritis in the other 12. Among the osteoporotic cases 9 were female and 3 male, and the ages varied between 52 and 70 years. This osteoporosis did not differ from postmenopausal osteoporosis. Hypertrophic changes occurred in 8 males and 4 females and the ages varied between 51 and 80. The authors conceived a theory to explain these findings. Bony changes

present in diabetes are not the result of diabetes in itself, but a hormonal dysfunction which would precede or coincide with diabetes. Decrease in gonadal function in old age as a result of decrease in gonadotropins would produce a compensatory increase of corticotropin responsible for the occurrence of diabetes and osteoporosis. If a compensatory increase of growth hormone predominates, then hypertrophic changes associated with diabetes would result. (French)

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Protas, Maurice (*George Washington Univ. Sch. of Med., Washington, D.C.*): MANAGEMENT OF DIABETES BEFORE, DURING, AND AFTER ANORECTAL AND COLON SURGERY. Am. J. of Proctology *5*:222-27, September 1954.

The diabetic patient under good control presents no serious problem for emergency or elective surgical intervention and may be expected to have as favorable a result and recovery as the nondiabetic patient. The anesthetic should be chosen to suit the individual case. Spinal anesthesia is the anesthetic of choice for the diabetic requiring colon surgery. A plan for the preoperative, operative, and postoperative management of diabetic patients undergoing surgery is presented.

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Randle, P. J. (*Dept. of Biochem., Univ. of Cambridge, Cambridge, England*): PLASMA-INSULIN ACTIVITY IN ACROMEGALY: ASSAYED BY THE RAT-DIAPHRAGM METHOD. Lancet *1*:441-44, Feb. 27, 1954.

The increased insulin-like activity of acromegalic plasma, assayed by the rat-diaphragm method, does not necessarily mean that acromegalic plasma contains more insulin than normal human plasma; for Ottaway observed that small amounts of growth hormone had an insulin-like effect in vitro on the glucose utilization of rat diaphragm, and the level of growth hormone in acromegalic plasma is likely to be high. The nature of the material responsible for the enhanced insulin activity of acromegalic plasma is being further investigated. The insulin-like activity of acromegalic plasma does not depend on the phosphorus content, because samples of acromegalic plasma with normal phosphorus content showed enhanced insulin activity. Discussion of the possible significance of these results in relation to the role of growth hormone in the secretion of insulin must be deferred until the nature of the factor in acromegalic plasma responsible for its increased insulin activity has been determined.

Robillard, R. (*Asst. Prof. Clin. Med., St.-Luc's Hospital, Montreal, Canada*): THE IMPORTANCE OF EDUCATION IN DIABETICS. Union méd. Canada, *83*:789-92, July 1954.

It is important for the diabetic to know that close maintenance of diet and insulin therapy will assure an aglycosuric urine compatible with good health. The combined efforts of physicians, dietitians, and nurses are necessary to attain this goal. (French)

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Rocha, A.: CONTRAINDICATION OF SUGAR-FREE DIETS IN CERTAIN CASES OF DIABETES. Rev. Espan. Enf. Del. Ap. Dig. Nutr. *12*:581-85, Nov.-Dec. 1953 (Abst. in Am. J. Digest. Dis. *21*:144, May 1954).

The author discusses the bases for contraindication of diets too low in carbohydrate in patients with diabetes mellitus. (Spanish)

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Rocha, Alfredo (*Spain*): CONTRAINDICATION FOR CARBOHYDRATE-RESTRICTED REGIMENS IN CERTAIN DIABETICS. Rev. Españ. Enferm. Ap. Digest. *12*:672, Nov.-Dec. 1953.

Sixty-three diabetic patients were studied and placed in two categories depending upon the level of cholinesterase found in the serum. In the first group, a low cholinesterase level, along with laboratory findings compatible with liver insufficiency, was found and called nonpancreatic type of diabetes with liver involvement. The second group showed a normal cholinesterase level and no evidences of liver damage and was called pancreatic type of diabetes. It is pointed out that a carbohydrate-restricted diet in the first group can be an aggravating factor in liver dysfunction. It is in this group that so-called insulin resistance is often found. A moderate carbohydrate-restricted diet and sufficient amount of insulin seem to be rational in the second group. (Spanish)

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Rodríguez, R. R. (*Institute de Biologia y Medicina Experimental, Costa Rica*): CURE OF ALLOXAN-DIABETIC RATS BY PROLONGED ADMINISTRATION OF ESTROGENS. Rev. Soc. argent. biol. *29*:255-65, Oct.-Nov. 1953.

Alloxan-diabetic rats were fed a special diet by forced-feeding and treated with estradiol benzoate (15 *u*g. per rat per day), alone or associated with insulin, for 6

months. The nontreated rats remained diabetic and some of them died during the 6-month observation period. Insulin administration had no curative action although the animals were in good condition. Treatment with estradiol alone cured 47 per cent of the rats, especially those with initial hyperglycemia not exceeding 250 mg. per 100 cc. Insulin-estradiol administration cured 69 per cent of the rats. The recovery of diabetes was accompanied by a fall of the insulin requirement from 7 to 0 units per rat per day, in 3 to 4 months of treatment. Histological examination showed only in the cured animals practically normal islets of Langerhans. (Spanish)

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Rothfeld, Ben; and Rodas, J. M. (*Med. Serv. V.A. Hosp., Perry Point, Md.*): DIABETES AND PANHYPOPITUITARISM. Ann. Int. Med. *41*:140-46, July 1954.

Seven cases of diabetes and pituitary insufficiency previously reported in the literature are briefly summarized. The present case was a 65-year-old man, who had diabetes treated with insulin for nine years. For one year he had progressive weakness, loss of hair growth and intolerance to cold. His skin was fine and extremely pale. The examination of his eyes showed a vitreous hemorrhage in the left and multiple large retinal hemorrhages in the right eye. Insulin treatment was discontinued. A glucose tolerance test eight days later was diabetic in type. A Thorn test was positive. Urinary assay for FSH showed less than 6.6 mouse units. Death occurred two hours after losing consciousness, despite glucose therapy. Autopsy showed necrosis of the pituitary, probably secondary to infarction of the anterior lobe, and marked generalized cerebral and coronary arteriosclerosis.

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Seaholm, J. Arthur (*Huron Road Hosp., East Cleveland, Ohio*): DIABETIC ACIDOSIS AND COMA. Journal of the Student American Medical Association *3*:21-23, Jan. 1954.

The author reviews the fundamental pathological physiology of diabetic acidosis and coma and outlines normal carbohydrate metabolism. Current problems of therapy are considered, together with suggested measures for minimizing these problems.

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Smith, Homer W. (*Dept. of Physiol., New York Univ. Coll. of Med., New York, N. Y.*): DE URINA. J.A.M.A. *155*:899-902, July 3, 1954.

The Hindus identified the disease diabetes mellitus by the name "honey urine." It had been observed that ants were attracted to the sweet urine.

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Storni, Horario J. (*Policlínico Eva Perón, Buenos Aires, Argentina*): TREATMENT OF DIABETIC COMA. Día med. *36*:1167-72, July 1, 1954.

Some considerations concerning the treatment of diabetic coma are presented. Careful examination to disclose complications and early treatment are emphasized as being of prime importance. Hourly evaluation of the clinical response is regarded as a guide to the therapy. (Spanish)

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Teng, Ching Tseng (*Dept. of Physiol. Baylor Univ. Coll. of Med., Houston, Tex.*): STUDIES ON CARBOHYDRATE METABOLISM IN RAT KIDNEY SLICES. I. METABOLISM OF GLYCEROL AND PYRUVATE. Arch. Biochem. *48*:409-14, Feb. 1954.

The metabolism of glycerol and pyruvate, singly or together, in rat kidney slices in vitro has been studied under aerobic and anaerobic conditions. The aerobic data were in substantial agreement with the results obtained in similar experiments with rat liver slices, which have been reported previously. The anaerobic results provided suggestive evidence that the dismutation of pyruvate furnished high-energy phosphates and hydrogen acceptors for the metabolism of glycerol. A possible explanation has been discussed.

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Vallejo, Arias: SOCIODIETETIC PROPHYLAXIS OF DIABETES. *Rev. Espan. Enf. Del. Ap. Dig. Nutr. 12*:559-70, Nov.-Dec. 1953 (Abst. in Am. J. Digest. Dis. *21*: 92, March 1954).

Certain exogenous factors accelerate the development of diabetes in a patient, one factor of which is food. The main aim of a prophylactic diet is to maintain the ideal weight of each patient. Dietary prophylaxis of diabetes cannot be applied to the general public but to those predisposed to the condition. The general practitioner is the main agent in prophylaxis of diabetes with his work directed first to the children of diabetic patients and then to the general population. (Spanish)

# EDITORIALS

## THE POSSIBLE NEUROGENIC ORIGIN OF DIABETES

The old question of neurogenic origin of permanent diabetes in the human again has been brought to consideration by Paton and Petch's report[1] of a case of association of diabetes mellitus and cerebral tumor. The patient was a 51-year-old man who had no family history of diabetes, who was not obese, and in whom the cardinal symptoms of polydipsia and polyuria were of three months' duration. The report suggests that diabetes mellitus was caused by a glioblastoma multiforme involving the hypothalamus.

As Paton and Petch point out, it is widely known that transient hyperglycemia and glycosuria may be caused by cerebrovascular accidents, cerebral trauma or meningitis, and rarely, by cerebral tumor. They mention four reported instances of diabetes mellitus associated with lesions in or about the third ventricle. The fact that diabetes mellitus occurs commonly, yet rarely is associated with hypothalamic disease, makes it highly improbable that the two diseases have a true etiologic relationship.

The recent studies of Bauer[2] are interesting in this respect. He collected records of 60 patients in whom the existence of hypothalamic disease had been established by autopsy. Fifty-one of them had neoplasms; only ten of these patients had glycosuria and had glucose tolerance tests performed. Only one patient had diabetes mellitus, a 67-year-old woman. In three cases, there was a delay in return of the blood sugar to normal during glucose tolerance tests; in three, the tests were normal; and in three the test curves were flat. The incidence of hyperglycemia approximates that of almost any adult group.

In this respect, records of the Cleveland Clinic are of interest. In the last 800 consecutive cases of *verified* tumors of the brain, the diagnosis of diabetes mellitus appears in the records of only three patients. Blood sugar tests were performed in all of the 800 patients, though it is uncertain that all tests which showed only slight elevations were recorded in the diagnoses. Incidentally, one of the three patients was a 56-year-old, 218-pound woman with a parasagittal meningioma which would seem to have little, if any, connection with hypothalamic dysfunction. Neither of the other two patients had lesions involving the hypothalamus except possibly by pressure. The first patient was a 54-year-old, 242-pound woman who had changes in the visual field and erosion of the posterior clinoid processes. Chromophobe adenoma was proved at operation. Headache had existed for five years, and diabetes had been known to exist for one year. The fasting blood sugar was 216 mg. per 100 ml. The second patient was a 47-year-old man with meningioma of the olfactory groove. In 1950, he weighed 230 pounds, and had a blood sugar level of 170 mg. per 100 ml. fasting. In 1951, the patient's weight was 180 pounds, and the fasting blood sugar was 88 mg. per 100 ml. No case of pituitary tumor with diabetes mellitus—excluding cases of acromegaly and the rare instance of basophil adenoma—has been found in our records of the past 10 years.

Laboratory data in other cases with proven tumors of the thalamus, hypothalamus, or of both, which may be of clinical interest are shown in table 1.

TABLE 1

Data in cases of tumors of thalamus and/or hypothalamus

| Diagnosis | Hypothalamic and 3rd ventricle involvement | Blood sugar Mg. per 100 cc. | Time relation to eating |
|---|---|---|---|
| 1. Glioma, optic thalamus | | 92 | ¾ hr. p.c. |
| 2. Glioma, optic thalamus | Yes | 88 | Fasting |
| 3. Glioma, optic chiasm | Yes | 88 | ? |
| 4. Glioma, left cerebral hemisphere | Yes? | 98 | ? |
| 5. Thalamic tumor type? | Yes? | 111 | 1 hr. p.c. |
| 6. Meningioma tuberculum sella | Pressure | 106 | 2 hr. p.c. |

Data in cases showing extensive involvement of the hypothalamus by infiltration of malignant growth appear in table 2.

TABLE 2
Data in cases of tumor involving the hypothalamus

| Diagnosis | Blood sugar Mg. per 100 cc. | Blood sugar Time relation to eating |
|---|---|---|
| 1. Glioblastoma multiforme | 94 | Fasting |
| 2. Glioblastoma multiforme | 87 | ? |
| 3. Pinealoma | 83 | 6 hr. p.c. |
| 4. Pinealoma | 73 | Fasting |
| 5. Oligodendroglioma | 100 | ? |
| 6. Malignant adenoma of the pituitary | 84 | Fasting |

Considering the very common incidence of diabetes in man and the rarity of the association with it of hypothalamic disease, it appears that the balance of evidence at present is distinctly weighted against the existence of any true etiologic relationship. It still remains to be proven, however, that hypothalamic disease never causes diabetes mellitus.

REFERENCES

[1] Paton, A., and Petch, C. P.: Association of diabetes mellitus with cerebral tumour. Brit. M. J. *1*:855-56, 1954.

[2] Bauer, H. G.: Endocrine and other clinical manifestations of hypothalamic disease; a survey of 60 cases with autopsies. J. Clin. Endocrinol. & Metab. *14*:13-31, 1954.

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Cleveland, Ohio

## *PROBLEMS OF AGING*

Problems of aging have taken on new importance in the United States in the last twenty-five years. These problems derive from the population changes which are the result of the combined influences of a declining birth rate, the extension of life expectancy and the cessation of immigration. Another factor of importance is industrialization. The substitution of power and machines for easily hand-operated tools in factory and on the farm have markedly increased the productive output of each worker. The result is that there are many more individuals in the labor force than have been able to be provided with useful jobs.

One of the great dividends of the spectacular march of science in the field of disease control and better understanding of human living has brought about a marked increase in the average life span of the American citizen. A number of leading authorities are of the opinion that the health, welfare, happiness and usefulness of the senior citizen in our nation is our number one problem. The medical profession and particularly those leaders who are responsible for direction of research and planning the curriculum of medical schools, should recognize a new dimension now of importance in the health and welfare of human beings, namely, aging.

In times past, when relatively few of the population attained three score years and ten, older people could be tolerated, if not loved. Aging may be defined, of course, as the element of time in living. The positive attitude concerns growth, evolution and maturation. The negative depressing aspect is that of atrophy, involution and decay, ending in final senility. Now with the advances in understanding of the mechanics and physiological balances of the human body, much can be done to accentuate the positive aspects of growth in aging and for the control of the deteriorations, many of which are preventable. Emphasis should be placed on the need for a better understanding of the internal and the external environments of human existence. There is also need for attention to the important difference between chronological age and biological aging.

With information of great potential importance to human living now coming into the ken of medical science, the profession must recognize the need for a clearer appreciation and more intimate and sympathetic understanding of the older human body and mind. During the past five years, an increasing number of significant contributions have been appearing in medical literature having to do with aging and older individuals. This is not alone a medical problem, or a social problem, or an economic problem or a cultural problem. It has many facets.

The present era of interest in problems of aging may be said to have been started by Aldred Scott Warthin's series of lectures at the New York Academy of Medicine in the autumn of 1928. From this, that small classic, entitled "Old Age the Major Involution," now out of print, was published. Following this, the work of Cowdry with his volume on "Problems of Aging," acted as a further stimulant to the field. Now, organized medicine and the various special fields are showing a greater interest in the medical problems and the social problems, also,

of our senior citizens.

In this issue of DIABETES are presented reviews of recent books on these subjects. There are now three journals devoted to topics on aging. The medical profession through its organized societies is setting up committees on geriatrics which are surveying the broad, general and specific needs of older men and women.

In the field of nutrition, metabolism and diabetes, there is much of interest and importance that touches on the aging of patients. The researches now being carried on in nutrition, stress and motivation will undoubtedly lead to a further extension of the life span. More and more individuals will be growing into the higher years of life. The medical profession must recognize this fact, and plan for a higher level of health with better control of the deteriorations and degenerations, which, in many instances, may be prevented.

EDWARD L. BORTZ, M.D.
Philadelphia, Pa.

# *BOOK REVIEWS*

LIVING THROUGH THE OLDER YEARS. *Edited by Clark Tibbitts. $2.00, pp. 193. The University of Michigan Press, Ann Arbor, Mich., 1949.*

PLANNING THE OLDER YEARS. *Edited by Wilma Donahue and Clark Tibbitts. $2.50, pp. 248. The University of Michigan Press, Ann Arbor, Mich., 1950.*

GROWING IN THE OLDER YEARS. *Edited by Wilma Donahue and Clark Tibbitts. $2.50, pp. 204. The University of Michigan Press, Ann Arbor, Mich., Jan. 1951.*

REHABILITATION OF THE OLDER WORKER. *Edited by Wilma Donahue, James Rae, Jr., Robert B. Berry. $3.25, pp. 200. The University of Michigan Press, Ann Arbor, Mich., 1953.*

HOUSING THE AGING. *Edited by Wilma Donahue. $3.75, pp. 280. The University of Michigan Press, Ann Arbor, Mich., 1954.*

OLDER PEOPLE TELL THEIR STORY. *By Woodrow W. Hunter and Helen Maurice. $1.00, pp. 99. The University of Michigan Press, Ann Arbor, Mich., Dec. 1953.*

The first of this series of six volumes from The University of Michigan Press contains eleven important papers on various aspects of aging written by distinguished authorities in sociology, biochemistry, physiology, psychiatry, economics and religion. The chapter titles include: "Biologic Aspects of the Aging Process," by Carl V. Weller, "The Personal Challenge of Aging: Biological Changes and Maintenance of Health," by Edward J. Stieglitz, "Changes in Psychological Processes with Aging," by Wilma Donohue and "Mental Hygiene of Old Age," by Moses Frohlich. This material makes interesting reading. The contributions by Weller and Stieglitz are worthy of reading many times over.

The second volume of the series carries on the spirit and extends the information bearing on problems of aging which was begun in the first. The authors review the various social, economic and housing problems which are brought into the picture for the older members of our population. The interaction between the health and attitudes of older individuals and society's use of them as a part of the laboring group of the nation is reviewed by a number of experts.

The third volume focuses attention on health, mental hygiene and education. This volume gives intensive consideration to the problems which older people have identified as the most crucial in their adjustment to aging. The majority of these articles present general information which has unfortunately been studied by too few people. The excellent review of the control of degenerative disease by Kountz discusses problems which medical science must face if degenerative disorders are to be brought under effective treatment.

The fourth volume includes reports of four conferences on rehabilitation attended by leaders from the fields of public health, government, social service groups and lay workers. The nature and magnitude of the rehabilitation problem are reported by Howard A. Rusk, the challenge of the disabled in the clinic by James W. Rae, Jr., and an analysis of geriatric rehabilitation by Lionel Z. Cosin.

The fifth volume presents topics presented at a conference on the housing of healthy, frail, sick and disabled older people. It was also aimed to promote interest in active support for good housing and neighborhood planning, and to assess the housing desires and needs

of aging individuals of varying social, economic and health status.

The sixth volume contains a report of a survey of the needs of older people undertaken in Grand Rapids, Mich., and recommendations for community action developed by a local forum on aging.

PROBLEMS OF AGING. *Edited by Nathan W. Shock, Ph.D., Chief, Section on Gerontology, National Heart Institute, National Institutes of Health, and The Baltimore City Hospitals, Baltimore, Md. $4.25, pp. 213. The Josiah Macy, Jr., Foundation, 1954.*

The vision of the Macy Foundation in organizing various conference programs for the informal discussion of problems in the medical and social sciences made it possible for the distinguished director of the Macy Foundation, Frank Fremont-Smith, to bring together at a three-day conference on problems of aging a group of some thirty scientists from the various fields of the basic sciences and clinical practice.

In his introductory remarks, Roy G. Hoskins, Chairman of the Conference, directed attention to the anatomy and physiology of the cell. In the session devoted to cellular structure Warren Andrew of the Bowman-Gray School of Medicine indicated that cells are important in the study of aging because they are the basic common denominator. He demonstrates alterations in structure of cells which appear with aging, including alterations in the nerve cells.

In the session concerned with biochemical studies, Bacon F. Chow of Johns Hopkins University discussed the nutritional aspects of growth. In the maintenance of normal life, biochemically speaking, a series of enzymatic reactions was taken as a foundation process. In aging biologically, there may either be an over-abundance or underproduction of certain tissue enzymes or proteins, and, concomitantly, an over-all imbalance of the necessary metabolites for subsequent reactions to maintain health.

In presenting the role of comparative physiology in studies of aging, F. Bourliere of the University of Paris School of Medicine discussed the aging of various species including warm-blooded and cold-blooded vertebrates. He showed that there is a different growth and aging pattern for each of the species, but the differences appear to be more that of tempo than of mode.

At the end of this little volume, packed with information of utmost importance, is a summary by Clive M. McCay of the Department of Nutrition of Cornell University. McCay emphasizes that the goal of gerontology is not merely the extension of the life span but, more especially, the creation of better health in the higher years.

CLINICAL PATHOLOGIC CONFERENCES OF COOK COUNTY HOSPITAL (Volume 1—Cardiovascular-Renal Problems.) *Edited by Hans Popper, M.D., Ph.D., Director, Department of Pathology, Cook County Hospital; Scientific Director, Hektoen Institute for Medical Research of the Cook County Hospital; Associate Professor of Pathology, Northwestern University Medical School, and Daniel S. Kushner, M.D., Associate Director of Medical Education, Cook County Hospital, Research Assistant, Hektoen Institute; Clinical Assistant in Medicine and Fellow in Pathology, Northwestern University Medical School. $5.00, pp. 324. The Blakiston Co., Inc., New York, N. Y., 1954.*

This book is replete with instructive discussions of interesting and unusual cases, presenting problems of the sort with which the physician treating diabetic patients must be familiar because of the frequent association of cardiovascular disorders with diabetes. The editor can be complimented on the excellent work he has done in preparing these discussions for publication. The illustrations are clear-cut and adequate. The references have been well selected.

As stated in the introduction, "The real purpose is not to arrive at the right diagnosis and thus succeed in a guessing game, but rather to present logical and constructive thought processes which the audience can follow, and to exercise medical logic." The physician who uses the book to browse through while waiting for patients and in spare time will profit greatly.

# Charles F. Bolduan

## His Role in the Attack on Diabetes As a Public Health Problem

*Herman O. Mosenthal, M.D.,* New York*

*"Any effort to understand where we are going depends very largely on a knowledge of where we have been."*
Edward R. Murrow

How or why Charles F. Bolduan first became interested in diabetes I have never found out. He began his active work in this field while he was Director of the Bureau of Health Education of the Department of Health of the City of New York. In this capacity, he was editor of the *Quarterly Bulletin* published by the Health Department and in its pages he frequently presented information regarding diabetes. Then in 1930 he arranged to have a communication submitted by the Health Department to the New York Academy of Medicine. He stated that at that time there were about 2,000 diabetes deaths registered annually in the city of New York, that the diabetes death rate was about 50 per cent higher than it had been 20 years previously and that these facts called for some remedial effort.

Acting on this suggestion, a subcommittee of the Committee on Public Health Relations of the New York Academy of Medicine was formed for the purpose of studying the problems presented by Dr. Bolduan. This committee included the following physicians: Charles F. Bolduan, Haven Emerson, James Ralph Scott, Henry J. Spencer and Herman O. Mosenthal, Chairman; additional members were E. H. L. Corwin, Ph.D., and Alice E. Paulsen, Ph.D. The results of the deliberations of the committee were published as the Hermann Michael Biggs Memorial Lecture delivered at the New York Academy of Medicine, April 6, 1933, by Dr. Herman O. Mosenthal and discussed by Drs. Bolduan, Elliott P. Joslin, Nellis B. Foster, and Louis I. Dublin. Subsequently, the results, elaborated a little further, were published in the *American Journal of Medical Sciences* under the title "Diabetes Mellitus—Problems of Present Day Treatment," by Drs. Herman O. Mosenthal and Charles F. Bolduan.

The report of the Committee on Diabetes of the New York Academy of Medicine included a recommendation that a diabetes association be formed. Before discussing further the organization of the New York Diabetes Association, consideration must be given to the previously existing attitude of the medical profession towards diabetes. Otherwise it would seem as though the Association originated in the way a white rabbit is drawn out of a conjurer's hat, without rhyme or reason and without purpose or objective.

A study of the diagnosis of diabetes as shown in the early records of the New York Hospital was made by Dr. Bolduan and Dr. Paulsen. In this hospital, one of the oldest of the leading hospitals in New York City, which included in its attending staff the most eminent physicians, little attention was given to diabetes in the nineteenth century. According to Bolduan, these records showed that urinalysis was uncommon 100 years ago—"I went over the 409 consecutive case histories of medical patients admitted between March 26 and Oct. 15, 1860. In only 63 case histories is there even mention of the character of the urine and in only 10 of these 63, does this state the results of a chemical test, namely the test for albumin. In the remaining 44 cases where the urine is mentioned the comments are limited to such phrases as 'scanty and high-colored,' or 'high-colored and acid,' or 'abundant and clear.' In not one of the 409 cases is there a single instance of a test of sugar and naturally not a single case of diabetes. . . . Out of 250 consecutive case histories in 1869, only 17 had any mention of the character of the urine and in 12 of these tests for albumin

*Dr. Mosenthal, first president of the New York Diabetes Association and second president of the American Diabetes Association, died on April 24, 1954.

were mentioned . . . again not a single test for sugar was recorded and of course not one case of diabetes. . .

"In 1880, some progress is evident. Compared with the histories of a decade before we find an increased proportion of tests made of the urine. Moreover, the examination always includes a microscopical examination. The chemical tests, to be sure, are limited to tests for albumin. Only in one instance, a case of diabetes, is presence of sugar mentioned. Out of 100 consecutive medical histories, 37 reported tests of the urine. . .

"The medical histories of 1890 reveal that routine tests of the urine for albumin, sugar and microscopic appearance have been inaugurated."

Previous to 1890, there was almost complete ignorance concerning the existence of diabetes in the United States. The disease was practically unrecognized by the laity and the medical profession. It was in 1906 that I first came in contact with diabetes as a disease. Previously it had been just an occasional case which I had seen and which I realized my medical instructors and consultants did not know much about. At that time I was taken under the wing of Dr. Theodore Janeway, who because one of his intimate friends developed severe fulminating diabetes, had become intensely interested in the condition. His office was organized so that Dr. William W. Herrick took charge of the new MacKenzie polygraphs which were being used in connection with heart disease and I studied the chemistry of metabolic disorders, including diabetes.

In 1912, I became convinced that a diabetes clinic was feasible and worth while and, consequently, at the Vanderbilt Clinic I began to treat diabetic cases. The past records of the Vanderbilt Clinic contained a careful index of thousands of patients but yielded only six cases of diabetes. At first I was working behind a screen, in the corner of a room, and felt amply rewarded if one patient attended on each weekly clinic day. However, the enterprise soon expanded and the patients were referred by many of the hospitals in New York City and from a radius of 40 miles outside of the City, when it became known that we were offering treatment for diabetes. Very soon we arrived at a roster of 60 patients and made up our minds that that was the total number we could handle. From this small beginning clinics have come up all over the area of Greater New York and throughout the United States. At the present moment, there are about 75 clinics devoted to the treatment of diabetes within the area of Greater New York and each one of these has an attendance of 50 patients or more. The large number of diabetes cases in New York City might be inferred from the fact that at Sea View Hospital, an institution devoted to the treatment of tuberculosis, there were usually about 90 patients whose tuberculosis was a complication of diabetes. The results at the Vanderbilt Clinic convinced us that ambulant treatment of diabetes was possible and saved the resources of the patients by doing away with their hospital bills and by keeping them at work. Insulin, of course, was not available at that time and yet we accomplished a great deal even without it.

A micro method for the determination of blood sugar, the Lewis-Benedict method, was introduced in 1913. By the use of very small amounts of blood, multiple evaluations of blood sugar could be made compared to only occasional ones when former procedures requiring large quantities of blood had to be employed. Similar methods were developed for other crucial substances in the blood. These discoveries opened pathways for the acquisition of knowledge concerning metabolic disorders. The immediate better understanding of the significance of blood sugar levels and of acidosis may be regarded as of especial importance in diabetes.

In 1914, Dr. Janeway took up his duties at the Johns Hopkins Medical School as first, full-time professor of medicine in the United States. He asked me to accompany him as an associate, especially to inaugurate a chemical laboratory having practical contact with the medical department. One of my duties was to establish a clinic for diabetes which soon had a considerable number of patients. The laboratory enabled my colleagues and me to do a great deal of work on diabetics and we divided our time about equally between diabetes, nephritis and hypertension. On returning to New York, I established a diabetes clinic at the then New York Post-Graduate Hospital, now University Hospital. Later my associates and I were ready to do our share of work in determining the action of insulin and its clinical application. The introduction of insulin in 1922 changed the whole outlook of physicians and patients in regard to this disease and instead of dreading it we became eager to establish the proper steps for its treatment.

In arranging for the organization of a diabetes association, Dr. Bolduan and I came to the conclusion that help was required in at least two directions; first, a certain amount of money was essential and second, experienced executive supervision of the project would be indispensable. About this time I had a chance to contact Mr. Lucius N. Littauer and with Dr. Bolduan's help succeeded in securing his support. He agreed to donate $5,000 a year for three years to start the project and

arrangements were made for affiliation with the New York Tuberculosis and Health Association. Following this, Dr. Bolduan suggested a comprehensive outline of the objectives of the association. Thus, the New York Diabetes Association came into being on Dec. 26, 1934.

During the first three years, the New York Diabetes Association was an affiliate of the New York Tuberculosis and Health Association. This arrangement was terminated when the funds donated by Mr. Littauer were exhausted. Dr. Bolduan again came to the rescue of the Association by asking his friend, Colonel Edward F. Brown, for his support. Accordingly, Colonel Brown granted the Association office space and he also provided methods for collecting small amounts of money from its supporters.

One of the important educational projects of the New York Diabetes Association was the publication of the so-called "Fundamental Concepts in the Treatment of Diabetes." These pamphlets were first published anonymously by the Committee on Internal Medicine of the New York Diabetes Association. Their publication, incorporated in successive issues of the *Quarterly Bulletin* of the New York Department of Health, was made possible through the courtesy of Dr. Bolduan.

A valuable exhibit entitled "Diabetes, a Public Health Problem," was prepared by Dr. Bolduan for the meeting of the American Medical Association in 1935. Later it was reproduced in miniature in a letter-sized pamphlet with brief articles, to supplement the charts written by Dr. Bolduan and Dr. Herman Lande. The Association shared with the New York Academy of Medicine the expense of preparation of cuts for the charts.

The formation of a national diabetes association was considered in the deliberations of the Committee on Diabetes of the New York Academy of Medicine, published in 1932. On a visit to Cincinnati some time later, I was consulted by Dr. Cecil Striker and Dr. William H. Muhlberg about the advisability of proceeding with the creation of such an association. It was the concensus that there was need for the organization and endorsement was secured from existing local diabetes associations including those of New York, Cincinnati and Philadelphia.

Dr. Bolduan took a constant interest in the plans and made many suggestions in regard to the formation of the American Diabetes Association. At a luncheon held in New York in June 1940 final steps were taken. Dr. Cecil Striker was elected president and Dr. Bolduan became a member of the Council. Dr. Bolduan served as a member of the Council of the American Diabetes Association from 1941 to 1944. He was elected an honorary member in 1944. Only two others had been honored in this way prior to this date, namely the discoverers of insulin, Sir Frederick Banting and Professor Charles H. Best.

Dr. Bolduan was born in Bielefeld, Germany, on May 7, 1873. He came to this country and attended the public schools of Brooklyn, New York. He received the degree of Graduate Pharmacist from the College of Pharmacy, New York City, and later he received the degree of Doctor of Medicine from the College of Physicians and Surgeons, Columbia University. His postgraduate medical work was carried on at the University of Berlin. His long and distinguished career in public health began in 1904 when he joined the staff of the New York City Department of Health as a bacteriologist. Three years later, he was promoted to the position of assistant to Dr. Hermann M. Biggs, general medical officer of the health department and one of the great pioneers in public health. In 1914, Dr. Bolduan organized and became the first Director of the Department's Bureau of Health Education, in which capacity he remained until 1918. In 1918 to 1928, he was with the United States Public Health Service, first as chief of the section on health education and later as a surgeon in the United States Consular Service in Europe. In 1928 he returned to the New York City Department of Health as Director of the Bureau of Health Information. When he retired on June 1, 1943, he had completed thirty-nine years of continuous service in the public health field.

No man ever worked more unselfishly and with less view to publicity than Dr. Bolduan. He always subordinated individual ambitions for the common good. He accomplished much for the education of the public and for the medical profession. The initiation of both the New York Diabetes Association and the American Diabetes Association originated to a large degree through the efforts of Charles F. Bolduan.

*ORGANIZATION SECTION*

## The Fifteenth Annual Meeting

The next Annual Meeting of the American Diabetes Association will be held in Atlantic City, N. J., on June 4-5, 1955. Our organization, as in the past, will hold its meeting immediately preceding the Annual Session, June 6-10, of the American Medical Association.

Chalfonte-Haddon Hall will serve as headquarters for our Association. Individual rooms are being held for members, but, as announced in previous issues of DIABETES, and in a memorandum to members of the Association Dec. 3, 1954, there is no assurance of sufficient accommodations for everyone. Members wishing to attend the Annual Meeting are urged to make their reservations immediately.

Those who wish to remain for the American Medical Association session must make reservations for June 6-10 through the Atlantic City Convention Bureau, 16 Central Pier, Atlantic City, N. J., either by letter or by filling out the reservation form appearing in the *Journal of the American Medical Association.* If you are planning to stay over for the A.M.A. session and do not wish to change hotels, The Convention Bureau has given reasonable assurance that reservations will be continued at Chalfonte-Haddon Hall if they are sent in promptly.

Scientific sessions of the American Diabetes Association Meeting will be held Saturday afternoon, June 4, and Sunday morning and afternoon, June 5. Physicians and other scientists are invited by Frederick W. Williams, M.D., Chairman of the Association's Commitee on Scientific Programs, to submit abstracts of papers which they would like to present at the Scientific Sessions. Persons interested are requested to submit eight copies of the abstracts to facilitate review of their material by the Committee.

## The Third Student-Intern Essay Contest

Two awards will be made in the Third Student-Intern Essay Contest sponsored by the American Diabetes Association. A prize of $250, made possible by the generosity of the St. Louis Diabetes Association, will be given to the author or authors of the best paper reporting original laboratory research or clinical study. An additional award of $50 will be given for the best review article or case report. It has been given anonymously by a member of the Association.

Candidates for either prize may select any subject relating to diabetes and basic metabolic problems. Manuscripts should be submitted by May 10, 1955, to the Editorial Office of DIABETES: *The Journal of the American Diabetes Association,* 1 East 45th Street, New York 17, N. Y.

The contest is open to medical students or physicians within two years of graduation. It is hoped that each year a larger number of young physicians will direct their study to diabetes and to the care of diabetic patients.

## Second Congress of the International Diabetes Federation

The British Diabetic Association, 152, Harley Street, London, W.1, will act as host at the Second Congress of the International Diabetes Federation to be held in Cambridge, England, July 4-8, 1955. Sir Lionel Whitby, C.V.O., M.C., Professor of Physic (Medicine), Cambridge University, will be Honorary President of the Congress.

There will be two sections of the Congress, one purely scientific for doctors and those in allied professions; the other for laymen, for discussion of social problems. Information about reservations and so forth may be secured from Mr. James G. L. Jackson, Secretary-General of the British Diabetic Association, who is acting as Organizing Secretary of the Congress. Information can also be secured from the National Office of the American Diabetes Association.

## New Members

*The following Active Members were elected as of November 1 and December 1, 1954:*

| | |
|---|---|
| *California* | |
| Sox, Harold C. | Palo Alto |
| *Idaho* | |
| Stein, Burton R. | Lewiston |
| *Kansas* | |
| Russell, Philip W. | Wichita |
| *Massachusetts* | |
| Adeson, Garvey | Pittsfield |
| *Michigan* | |
| Harroun, John E. | Owosso |
| Moffitt, Raymond E. | Detroit |
| *Minnesota* | |
| Chiles, Noah H. | Rochester |
| *New Jersey* | |
| Dresdale, Frank C. | Plainfield |

| | |
|---|---|
| Major, Morton | Atlantic City |
| Pellegrino, Edmund D. | Flemington |
| *New York* | |
| Alessi, Alfred C. | Niagara Falls |
| Bernstein, Morley L. | Niagara Falls |
| Connelly, John J. | Niagara Falls |
| Dake, Charles M., Jr. | Niagara Falls |
| D'Errico, Joseph A. | Niagara Falls |
| Gillick, William C. | Niagara Falls |
| Glennie, Robert D. | Niagara Falls |
| Goetzman, Arthur C. | Niagara Falls |
| Goodkin, George | New York |
| Grabiec, Max V. | Niagara Falls |
| Graef, Irving | New York |
| Hart, Joseph C. | Poughkeepsie |
| Jones, Glenn E. | Niagara Falls |
| Leone, John A. | Niagara Falls |
| Lewis, William R. | Niagara Falls |
| Magiday, Morton | New York |
| Reif, Fritz B. | Niagara Falls |
| Schiff, Lester | Niagara Falls |
| Shoemaker, Edwin A. | Niagara Falls |
| Taylor, Donald E. | Niagara Falls |
| *Ohio* | |
| Stevers, Charles L. | Toledo |
| *Oklahoma* | |
| West, Kelly McG. | Oklahoma City |
| *Pennsylvania* | |
| Wornas, Christian G. | Reading |
| *Tennessee* | |
| Lentz, Julian C., Jr. | Maryville |
| *Washington* | |
| Larson, Evrel A. | Bellingham |
| *West Virginia* | |
| Weier, Karl E. | Bluefield |

OTHER COUNTRIES

| | |
|---|---|
| *Argentina* | |
| Jauregui, Guillermo R. | Buenos Aires |

*The following Associate Member was elected as of December 1, 1954:*

| | |
|---|---|
| Scanlon, Alice | Wethersfield, Conn. |

# News Notes

## Goldberger Medal Awarded to Dr. Russell Wilder

Russell M. Wilder, M.D., former Professor of Medicine, University of Minnesota (Mayo Foundation) and Head of the Mayo Clinic's Department of Medicine, received the American Medical Association's Joseph Goldberger Award in clinical nutrition on November 5. The award was presented at the Annual Meeting of the Food and Nutrition Board of the National Research Council in Washington, D. C. The gold medal and $1,000 were given to him by Grace Goldsmith, M.D., New Orleans, a member of the A.M.A.'s Council on Foods and Nutrition.

Dr. Wilder participated in the organization of the Food and Nutrition Board of the National Research Council in 1940 and was its first chairman. He remained a member of the board until 1950. He also was a member of the A.M.A.'s Council on Foods and Nutrition from 1933 through 1951.

## Symposium on Diabetes

"Results of Recent and Current Studies from New England Deaconess Hospital, Boston, Mass.," will be presented in a Symposium on Diabetes at The New York Academy of Medicine Tuesday evening, January 18. Presentations include: "Cost of Treatment and Rehabilitation of Patients with Foot Lesions. A Co-operative Study of 500 Cases in Boston Hospitals, 1953-54," by Howard F. Root, M.D.; "The Value of Control of Diabetes (with Presentations of Patients)," by Elliott P. Joslin, M.D.; "Pregnancy in Diabetes: Results of Recent Experience," by Priscilla White, M.D.; "Behavior of Phosphorus in the Deposition of Liver Glycogen," by Nancy Nichols, M.D.; "Attempts to Alter the Trend of Diabetes in Young Patients: Preliminary Report," by Priscilla White, M.D.; "Experience with Lente Insulin," by Alexander Marble, M.D.; "Recent Data Regarding Mortality and Causes of Death in Diabetes," by Herbert H. Marks, Metropolitan Life Insurance Company. Edward Tolstoi, M.D., is Chairman of the Section on Medicine, which is presenting the Symposium, and Charles A. Poindexter, M.D., is Secretary.

## Personals

Joseph T. Beardwood, Jr., M.D., and Henry B. Mulholland, M.D., were guest speakers at a Diabetes Assembly in Orlando, Fla., October 21-22. Dr. Beardwood's subjects included: "Diabetic Ketosis, Treatment and Prevention," "New Views on Pathology of Diabetes," "Use of Corticotropic Hormones in Diabetes," "Hemochromatosis, Newer Concepts in Etiology and Treatment," and "The Juvenile Diabetic Patient."

Dr. Mulholland spoke on the following subjects:

"Diabetes—Its General Management," "Radioactive Isotopes in the Diagnosis and Treatment of Thyroid Disease," "Some of the Complications of Diabetes," "Preoperative and Postoperative Care of the Diabetic Patient," "Indications for Various Insulins and their Use," and "Cardiovascular Complications."

Drs. Beardwood and Mulholland also took part in a panel discussion and a public meeting October 22.

T. Z. Cason, M.D., and Richard H. Sinden, M.D., were member speakers at the Assembly. Dr. Cason spoke on "Twenty-five Years' Clinical Practice of Diabetes," and Dr. Sinden on "Neurologic Lesions as Observed by the Clinician." They also took part in the panel discussion.

Harold Brandaleone, M.D., appeared in "Heartbeat in Industry," on the Mutual Broadcasting Company network November 7, and on WOR (New York) November 14.

Jerome W. Conn, M.D., Ann Arbor, Mich., President, presided at the Annual Meeting of the Central Society for Clinical Research held October 29-30 in Chicago. Dr. Conn was Vice President last year and for three years prior was a member of the Council of that organization. Randall G. Sprague, M.D., Rochester, Minn., was elected Vice President for 1955.

William R. Kirtley, M. D., of Indianapolis, Ind., was one of the thirty-three newly-elected members at the 1954 Annual Meeting.

Bernardo Houssay, M.D., Nobel Prize winner, President of the Argentine Association for the Advancement of Science and the Argentine Biological Society, Buenos Aires, Argentina, was awarded an honorary Doctor of Science Degree at the Columbia University Bicentennial Convocation on October 31.

Laurance W. Kinsell, M.D., Oakland, Calif., was co-author of a paper, "Anesthesia and Management During Hypophysectomy for Fulminant 'Juvenile' Diabetes," delivered October 25 at the annual meeting of The American Society of Anesthesiologists in Cincinnati.

Brigadier General Alexander Marble of the Joslin Clinic, Boston, is one of five members of a Council of General Officers from the Army Medical Corps Reserve organized in November to advise the Surgeon General on matters related to the Medical Reserve. Organization of the Council was announced by Major General George E. Armstrong, Surgeon General, The Department of the Army.

James M. Moss, M.D., Georgetown University School of Medicine, Washington, D. C., won second prize for his exhibit, "The Symptoms of Diabetes Mellitus," at the First Interstate Scientific Assembly of The Medical Society of the District of Columbia and The Medical Society of Virginia held in Washington November 1-3, 1954. Details about the Assembly, and Dr. Moss' exhibit, were reported in the September-October issue of DIABETES.

The Commissioner of Health of The City of New York announces the opening of the Brownsville Diabetes Control Center in the Brownsville District Health Center, 259 Bristol Street, Brooklyn, N. Y., on Nov. 18, 1954. George Anderson, M.D., Chairman, Diabetes Committee of the Medical Society of the County of Kings; Morris Ant, M.D., Past-President, East New York Medical Society; Norman Jolliffe, M.D., Director, Bureau of Nutrition, Department of Health; and Henry E. Marks, M.D., Vice President, New York Diabetes Association, are members of the Medical Advisory Committee. The Staff includes Louis Boas, M.D., Consultant. Speakers for the November 18 program included George Anderson, M.D., "Uncontrolled Diabetes—Complications and Disabilities"; Morris Ant, M.D., "Education of the Public in the Prevention and Control of Diabetes"; and Henry E. Marks, M.D., "Screening Programs for the Detection of Diabetes."

## Obituary

Louis Bauman, M.D., died November 1 in New Rochelle Hospital at the age of 74. Dr. Bauman, retired Assistant Professor of Clinical Medicine at Columbia University, was a graduate of Columbia University's College of Physicians and Surgeons in 1901, and studied at the University of Berlin from 1905-1908. He joined the Columbia faculty in 1920 and retired in 1946. He had also been an attending physician at Presbyterian Hospital since 1920. Dr. Bauman also served on the faculties of the University of Iowa, and McGill University. He was at one time Chairman of the Clinical Society of the New York Diabetes Association and a member of the American Society for Clinical Investigation, and the American Society of Biological Chemists. Dr. Bauman's practice was limited to internal medicine. He is survived by a daughter, Mrs. Elfrieda M. Eckels, and a son, William A. Bauman, M.D.

# SUBJECT INDEX

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# Errata

p. 5 Hoet, J. P. In column 1, first line should read: *islets, hyperglycemia will appear;*

p. 56 Bucht, Härje, & others. Bibliographic reference should read: *Nord. Mec. 49:468-70, March 27, 1953.*

p. 59 Ingle, D. J., & others. In journal title, *Purmalis, Andrejo* should read *Purmalis, Andrejs.*

p. 60 Johnson, Doris. Title should read: *Dietotherapy: Planning the Modern Diabetic Diet.*

p. 62 Mosenthal, H. O. Title should read: *Insulin and Diabetes: Endogenous and Exogenous Insulin.*

p. 63 Needleman, H. L., & Horwitz, Orville. In journal title, *Cuteneous* should read *Cutaneous.*

p. 63 Needleman, H. L., & Horwitz, Orville. In twenty-second line, curtaneous should read cutaneous.

p. 65 Pasquinelli, F., & Calzolari, G. In thirteenth line, *preceeding* should read *preceding.*

p. 65 Prokhovnik, S. J., & Nelson, J. F. Bibliographic reference should read: *Australian J. Exper. Biol. & M. Sc. 31:279-82, June 1953.*

p. 68 Segaloff, Albert, & Horwitt, B. N. In third line, *streoisomer* should read *stereoisomer.*

p. 69 Sinkoff, M. W., & de Bodo, R. C. Bibliographic reference should read: *Arch. exper. Path. u. Pharmakol. 219:100-10, May 1953.*

p. 69 Sinkoff, M. W., & de Bodo, R. C. In journal title, *in* should read *an.*

p. 71 Stadie, W. C., & others. In twelfth line, *signficance* should read *significance.*

p. 72 Svanteson, Gunnar. Fifth line should read: *thirty-sixth week; (3) transfer of the infant to a.*

p. 73 Treadwell, C. R., & Dury, Abraham. In journal title, *Epinephine* should read *Epinephrine.*

p. 75 Wick, A. N., & Drury, D. R. In seventh and eighth line, delete *had little effect on the glucose oxidation and requirement.*

p. 141 Bachrach, W. H. In second line, *secretary* should read *secretory.*

p. 144 Craig, J. W., & others. In eighth line, delete *by either route.*

p. 151 Metropolitan Life Insurance Co. In fifteenth line, delete *not.*

p. 152 Mirsky, I. A., & others. In journal title, *Quantitive* should read *Quantitative.*

p. 235 Goldfarb, A. R., & others. At end of ninth line, insert *seems to indicate that most of the.*

p. 235 Goodman, J. I. At end of thirty-fifth line, insert *administration.*

p. 247 Searle, G. L., & others. In seventh line, *of* should read *to.*

p. 248 Tolstoi, Edward, & others. In sixth line, *therafter* should read *thereafter.*

p. 317 Kyle, L. H., & others. In fifth line, insert *defective* before *reabsorption.*

p. 318 Loyke, H. F., & Hoobler, S. W. In journal title, *of* should read *on.*

p. 365 Lukens, F. D. W. In fifth line, *queston* should read *question.*

p. 389 Baird, I. Mc., & Munro, D. S. In first line, *cause* should read *case.*

# AUTHOR INDEX

**In this Index are the names of the authors of articles which have appeared in DIABETES and those whose articles have been abstracted in the Journal during 1954. The asterisk (*) preceding the page reference indicates that the article appeared in full in DIABETES.**

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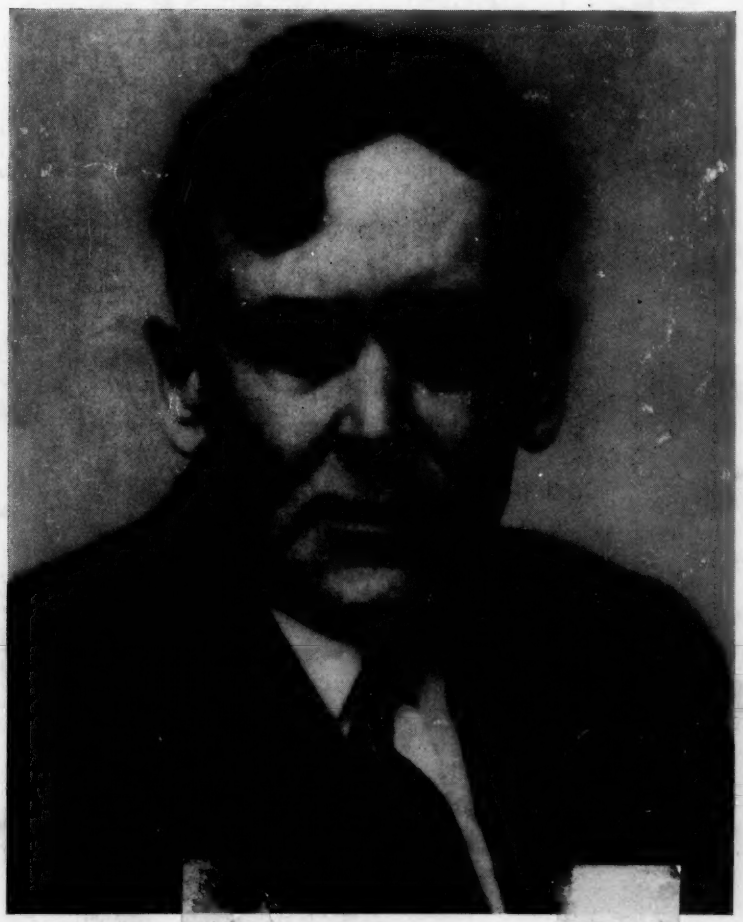

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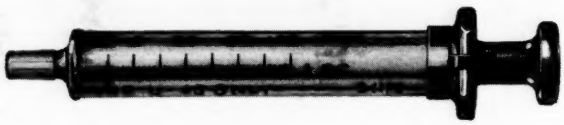

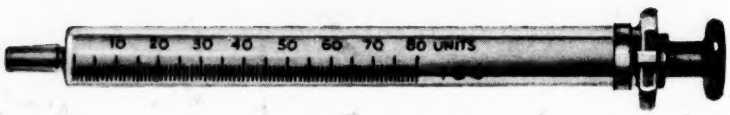


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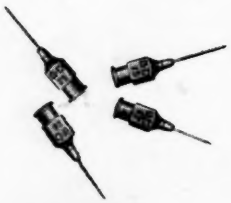

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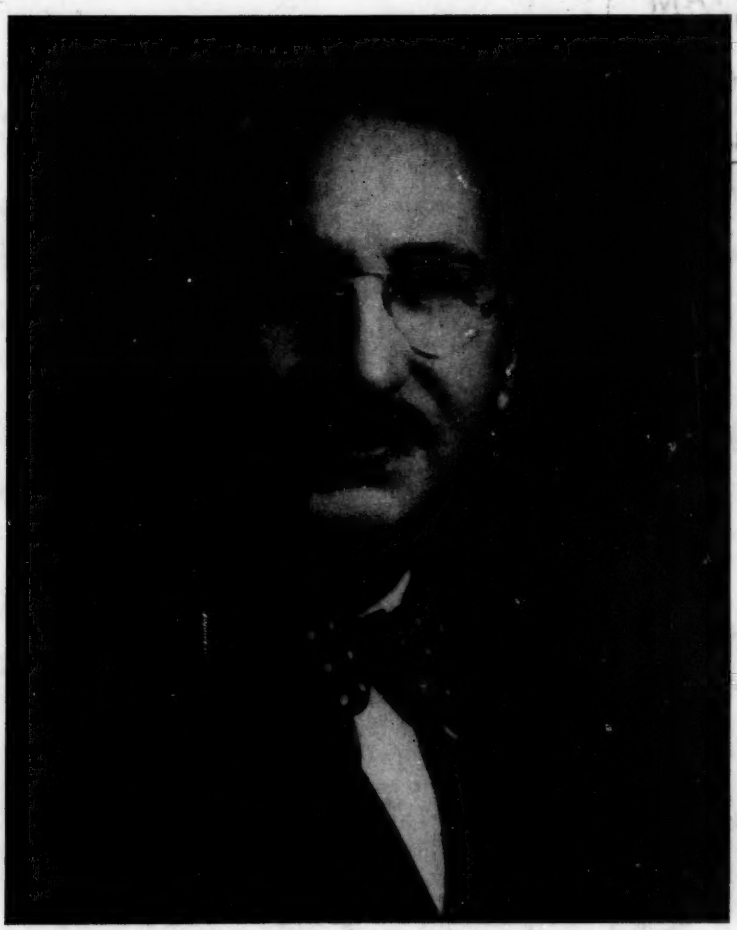

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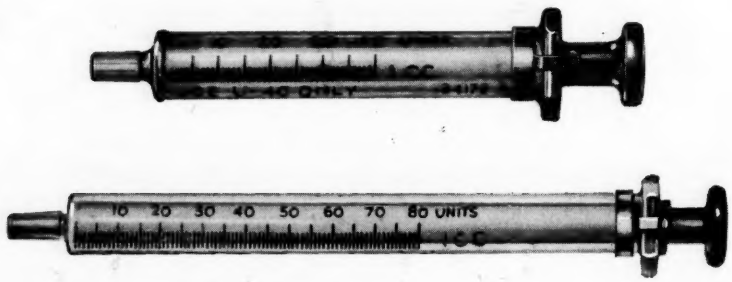


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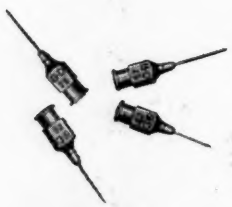

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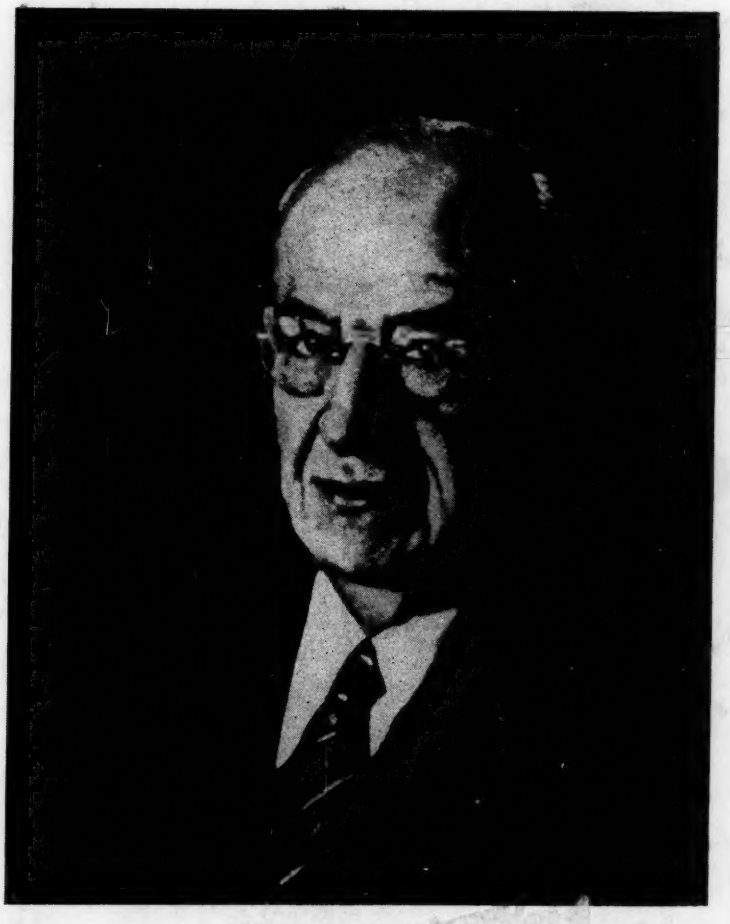

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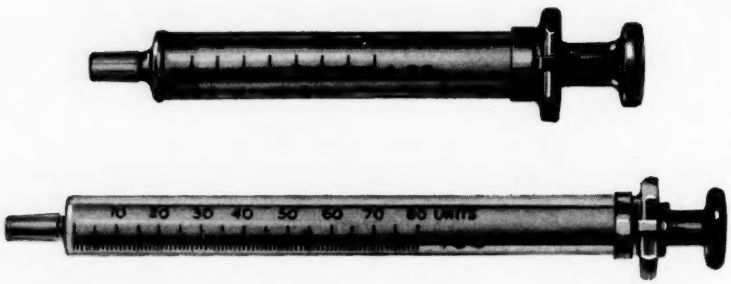


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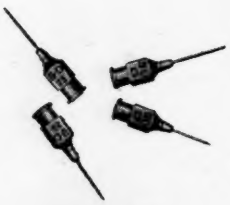
**for maximum safety, convenience and comfort**

B-D DIABETIC SUPPLIES are designed to make self-injection by your patients as safe, painless and convenient as possible.

**B-D Insulin Syringes:** Individually gauged and certified for accurate dosage—scale markings fused on the glass—different scales and color markings simplify accurate administration of varying strengths of insulin.



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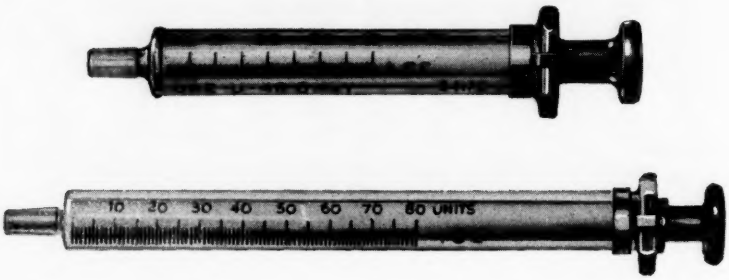


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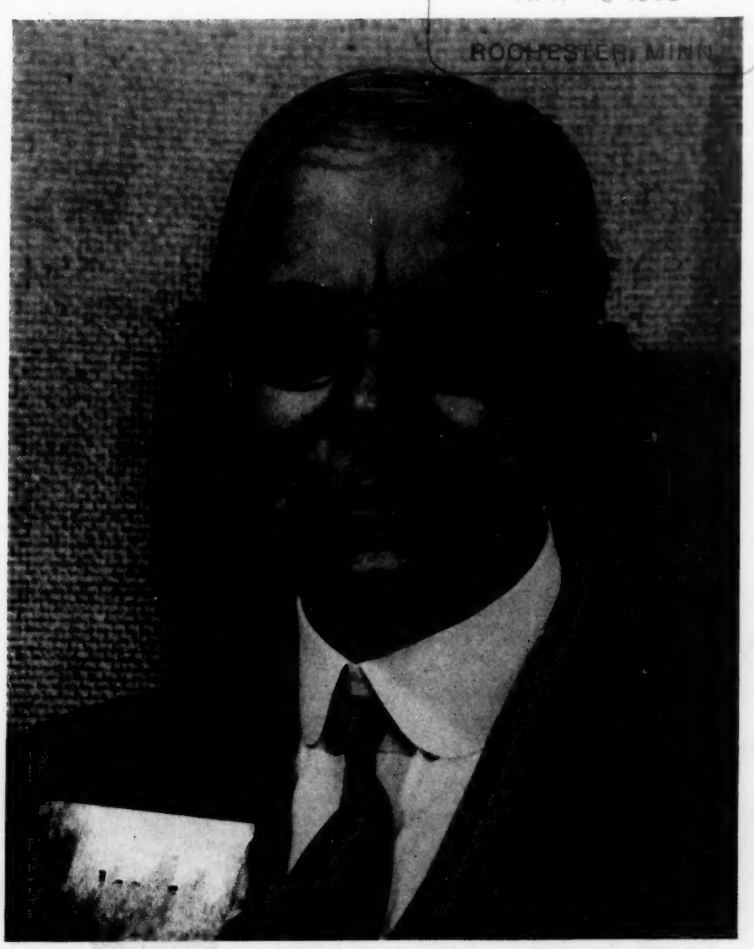

CHARLES F. BOLDUAN

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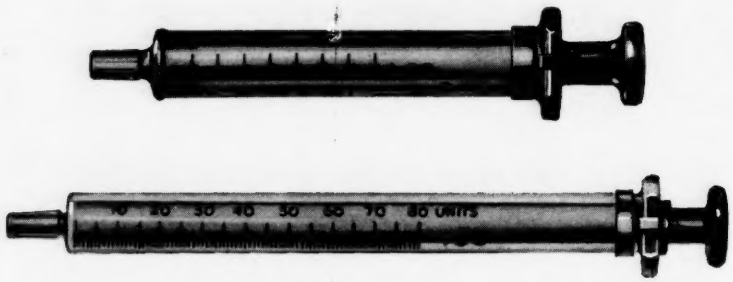

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